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BY AMIDINO GROUP SUBSTITUTED HETEROCYCLIC DERIVATIVES AND THEIR USE AS ANTICOAGULANTS

Abstract:

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The present invention relates to novel biheterocyclic derivatives which are factor Xa inhibitors; the pharmaceutically acceptable salts and *N*-oxides thereof; their uses as therapeutic agents and the methods of their making.

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BY AMIDINO GROUP SUBSTITUTED HETEROCYCLIC DERIVATIVES AND THEIR USE AS ANTICOAGULANTS

This application is based on U.S. Provisional Application Serial Number 60/072,654 filed on November 26, 1997.

THE INVENTION

This Application relates to compounds and compositions for treating diseases associated with serine protease activity, particularly factor Xa activity.

DESCRIPTION OF THE FIELD

Hemostasis is a function of the physiological processes which initiate and modulate blood coagulation and fibrinolysis. Blood coagulation involves a series of highly complex, inter-related proteolytic events which culminate in the formation of a fibrin clot surrounding the platelet aggregate which makes up the primary hemostatic plug that forms to prevent loss of blood when a vessel is damaged. Fibrin is the product of a proteolytic reaction catalyzed by thrombin, a serine protease, which in turn is the product of a proteolytic activation of prothrombin by factor Xa, also a serine protease. Thrombin also is a potent activator of platelet aggregation.

Factor Xa is converted from inactive factor X by two distinct mechanisms referred to as the intrinsic and extrinsic coagulation pathways. The intrinsic pathway comprises a series of proteolytic reactions catalyzed by factors originating in blood and culminates in the formation of factor IXa. The extrinsic pathway comprises the activation of factor VII by tissue factor, a membrane bound protein, which is available at the site of vessel injury and culminates in the formation of factor VIIa. Factor IXa and factor VIIa, in concert with tissue factor, catalyzes the conversion of factor X to factor Xa. Thus, the formation of factor Xa represents a convergence of the intrinsic and extrinsic pathways in the cascade of events which lead to blood coagulation.

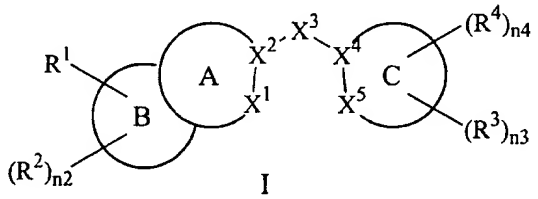
Fibrinolysis is the mechanism by which the platelet aggregate and fibrin clot is dissolved after the vessel injury has healed. The normal physiological condition results in an equilibrium between blood coagulation and anticoagulation mechanisms preventing hemorrhage while maintaining blood fluidity. A pathological condition leading to the occlusion of a blood vessel, i.e., thrombosis, is the equilibrium tipped in the direction of procoagulation. Arterial thrombosis which deprives tissue of oxygen will result in

ischemic necrosis of that tissue. Venous thrombosis may result in a pulmonary embolism. Agents which shift the equilibrium towards anticoagulation provide a method for treating and/or preventing thrombosis. Agents which inhibit factor Xa provide a valid pharmacological mechanism for effecting anticoagulation.

The disclosures of these and other documents referred to throughout this Application are incorporated herein by reference.

SUMMARY OF THE INVENTION

This Application relates to a compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from -N=, $-NR^5-$, -O- and -S-, wherein R^5 is $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and

X^5 is a heteroatom moiety selected from -N=, -NR^5-, -O- and -S-, wherein R^5 is as defined above, and any carbocyclic ketone, thioketone and iminoketone derivative thereof;

X^3 is -O-, -S-, -C(O)-, -NR^7-, -SiR^7R^8- or -CR^7R^8-, wherein R^7 is hydrogen, (C_{1-6})alkyl or hydroxy and R^8 is -R^6 or -X^6-R^6, wherein X^6 and R^6 are as defined above, or R^7 and/or R^8 together with a free valence on the annular atom adjacent to X^4 forms (C_3)alkylene;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any annular atom with an available valence comprising B;

each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently -R^6 or -X^6-R^6, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from (C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo, hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; with the proviso that R^2, R^3, R^4, R^5, R^7 and R^8 are not all hydrogen and/or (C_{1-3})alkyl when A together with B comprises 1*H*-benzoimidazol-2yl, C comprises 1*H*-benzoimidazol-2yl and X^3 is -CR^7R^8-; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

A second aspect of this invention is a pharmaceutical composition which contains a

compound of Formula I or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof in admixture with one or more suitable excipients.

A third aspect of this invention is a method of treating a disease in an animal in which anticoagulation can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof.

A fourth aspect of this invention is the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivative, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof as set forth in "Detailed Description of the Invention".

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the meanings given this Section:

"Alicyclic moiety" means any saturated or unsaturated, monocyclic or polycyclic portion of a radical and includes cycloalkyl, cycloalkylene, heterocycloalkyl and heterocycloalkylene, as defined in this Section. For example, alicyclic moiety refers to cycloalkyl as well as to the alicyclic portions comprising cycloalkylalkyl, cycloalkyloxy, cycloalkylcarbonyl, cycloalkylcarbamoyl, polycycloaryl, and the like.

"Aliphatic moiety" means any straight or branched, saturated or unsaturated portion of a radical and includes alkyl, alkylene, heteroalkyl and heteroalkylene, as defined in this Section. For example, aliphatic moiety refers to alkyl as well as to aliphatic portions comprising alkyloxy, arylalkyl, alkylcarbamoyl, and the like.

"Alkyl" means a straight or branched, saturated or unsaturated aliphatic radical

having the number of carbon atoms indicated, and any ketone, thioketone or iminoketone derivative thereof (e.g., (C_{1-6})alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl,

2-propynyl, 3-oxopentyl, 3-thioxopentyl, 3-iminopentyl, etc.).

"Alkylene" means a saturated or unsaturated divalent radical having the number of carbon atoms indicated and any ketone, thioketone, iminoketone and substituted derivative thereof (e.g., (C_{1-10})alkylene includes methylene (-CH_2–), ethylene (–CH_2CH_2–), methylethylene, vinylene, ethynylene, trimethylene (–$CH_2CH_2CH_2$–), 2-oxotrimethylene (–$CH_2C(O)CH_2$–), 2-thiatrimethylene (–$CH_2C(S)CH_2$–), 2-iminotrimethylene (–$CH_2C(NH)CH_2$–), propenylene (–CH_2CH=CH– or –CH=$CHCH_2$–), propanylylidene (=$CHCH_2CH_2$–), propendiylene (=CHCH=CH–), 1-aminotetramethylene, pentamethylene, etc.).

"Alkyloxy" means the radical –OR, wherein R is alkyl as defined above, having the number of carbon atoms indicated (e.g., (C_{1-6})alkyloxy includes the radicals methoxy, ethoxy, propoxy, isopropoxy, butoxy, *sec*-butoxy, isobutoxy, *tert*-butoxy, vinyloxy, allyloxy, 1-propenyloxy, isopropenyloxy, 1-butenyloxy, 2-butenyloxy, 3-butenyloxy, 2-methylallyloxy, ethynyloxy, 1-propynyloxy, 2-propynyloxy, etc.).

"Alkylsulfonyl" and "alkylthio" mean the radicals –$S(O)_2$R and –SR, respectively, wherein R is alkyl as defined above, having the number of carbon atoms indicated (e.g., (C_{1-6})alkylsulfonyl includes methylsulfonyl, ethylsulfonyl, propylsulfonyl, isopropylsulfonyl, butylsulfonyl, *sec*-butylsulfonyl, isobutylsulfonyl, *tert*-butylsulfonyl, vinylsulfonyl, allylsulfonyl, 1-propenylsulfonyl, isopropenylsulfonyl, 1-butenylsulfonyl, 2-butenylsulfonyl, 3-butenylsulfonyl, 2-methylallylsulfonyl, ethynylsulfonyl, 1-propynylsulfonyl, 2-propynylsulfonyl, etc.).

"Amidino" means the radical –$C(NH)NH_2$.

"Amino" means the radical –NH_2.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, etc.) and non-mammals (e.g., birds, etc.).

"Aryl" means an aromatic monocyclic or fused polycyclic radical containing the

number of annular carbon atoms indicated, wherein each ring contained therein is comprised of 6 annular members (e.g., (C_{6-14})aryl includes phenyl, naphthalenyl, anthracenyl, phenanthrenyl, etc.).

"Arylene" means an aromatic monocyclic or fused bicyclic divalent radical containing 6 to 10 annular atoms, wherein each ring contained therein is comprised of 6 annular members (e.g., arylene includes 1,4-phenylene, 1,2-phenylene, 1,5-naphthalenylene, 1,8-naphthaleylene, etc.).

"Aromatic moiety" means any aromatic portion of a radical and includes aryl and heteroaryl, as defined in this Section. For example, aromatic moiety refers to aryl as well as the aromatic portions comprising arylalkyl, polycycloaryl, and the like.

"Carbamoyl" means the radical $-C(O)NH_2$.

"Carboxy" means the radical -C(O)OH.

"Cyano" means the radical –CN.

"Cycloalkyl" means a saturated or unsaturated, monocyclic or fused polycyclic radical containing the number of annular carbon atoms indicated, wherein each ring contained therein is comprised of 3 to 8 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{3-14})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, etc.).

"Cycloalkylene" means a saturated or unsaturated, monocyclic or fused bicyclic divalent radical containing 3 to 14 annular atoms, wherein each ring contained therein is comprised of 3 to 8 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., cycloalkylene includes cyclopropylene, cyclobutylene, cyclopentylene, cyclohexylene, cyclohexenylene, 2,5-cyclohexadienylene, bicyclo[2.2.2]octylene, oxocyclohexylene, dioxocyclohexylene, thiocyclohexylene, 2-oxobicyclo[2.2.1]heptylene, etc.).

"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition which may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Fused heteropolycyclic radical" includes "fused heterobicyclic radical" and means a heterocyclic radical containing two or more rings having the number of annular members indicated, wherein at least two annular members of one ring are common to a second ring (e.g., a heteropolycyclic radical containing from 8 to 18 annular atoms and the carbocyclic ketone and thioketone derivatives thereof includes 1*H*-benzoimidazol-2-yl, 1*H*-naphtho[2,3-*d*]imidazol-2-yl, 1*H*-imidazo[4,5-*f*]quinolin-2-yl, 1*H*-imidazo[4,5-*b*]pyridin-2-yl, 1*H*-phenanthro[9,10-*d*]imidazol-2-yl, 1*H*-imidazo[4,5-*g*]quinoxalin-2-yl, 2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-yl, 2,6-dithioxo-2,3,6,9-tetrahydro-1*H*-purin-8-yl, 7*H*-purin-8-yl,

1,6-dihydrocyclopentaimidazol-2-yl, 4-quinolin-2-yl, etc.)

"Guanidino" means the radical $-NHC(NH)NH_2$.

"Halo" means fluoro, chloro, bromo or iodo.

"Heteroatom" means an atom selected from N, O, S and P.

"Heteroatom moiety", unless indicated otherwise, means a moiety selected from $-N=$, $-NR^9-$, $-O-$, $-S-$, $-S(O)-$, $-S(O)_2-$, $-P(O)(OR^9)-$, wherein R^9 is hydrogen or (C_{1-6})alkyl.

"Heteroalkyl" means alkyl, as defined above, except one or more of the carbon atoms indicated is replaced by a heteroatom moiety, as defined in this Section, and any ketone, thioketone or iminoketone derivative thereof (e.g., hetero(C_{2-12})alkyl includes methoxy, ethoxy, ethylthio, 2-(2-methoxyethoxy)ethoxy, 3-methoxymethoxycarbonylmethoxy, 2-(*N*-ethyl-*N*-methylamino)ethyl, 2-ethyliminoethyl, ethoxymethoxyphosphoryloxy, etc.).

"Heteroalkylene" means alkylene, as defined above, except one or more of the carbon atoms indicated is replaced by a heteroatom moiety, as defined in this Section, or any suitable combination thereof (e.g., $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^9)S(O)_2-$, $-S(O)_2NR^9-$, $-OP(O)(OR^9)O-$, and the like, wherein R^9 is hydrogen or (C_{1-6})alkyl), and any ketone, thioketone or iminoketone derivative thereof (e.g., hetero(C_{2-10})alkylene includes azaethylene ($-CH_2NH-$), 2-azapropenylene ($-CH_2N=CH_2-$), 1-oxatrimethylene ($-CH_2CH_2O-$), 2-oxo-3-azapentamethylene, 3-aza-2-thiopentamethylene, 2-oxa-3-oxopentamethylene, 3-aza-2-iminopentamethylene ($-CH_2CH_2NHC(NH)CH_2-$), 2,4-aza-2-methyl-3,3-dioxo-3-thiapentamethylene ($-CH_2NHS(O)_2N(CH_3)CH_2-$), 3-hydroxy-2,4-oxa-

3-oxo-3-phosphapentamethylene (-$CH_2OP(O)(OH)OCH_2$-), 3-aza-2-oxo-4-carboxyhexamethylene, 4-aza-1-oxa-3-oxohexamethylene, 1-thia-3-oxo-4-azahexamethylene, 1-thia-1,1,3-trioxo-4-azahexamethylene (-$CH_2CH_2NHC(O)CH_2S(O)_2$-), 3-aza-4-oxoheptamethylene, 1,4,7-trioxaoctamethylene, 6-aza-1-oxa-2,5-dioxooctamethylene (-$CH_2CH_2NHC(O)CH_2CH_2C(O)O$-), 3-aza-4-oxodecamethylene, etc.).

"Heteroaryl" means an aromatic monocyclic or fused polycyclic divalent radical having the number of annular atoms indicated, wherein each ring contained therein is comprised of 5 to 6 annular members and one or more of the annular atoms is a heteroatom moiety selected from -N=, -NR^9-, -O- or -S- and each ring contained therein is comprised of 5 to 6 annular members (e.g., hetero(C_{5-14})aryl includes thienyl, furyl, pyrrolyl, pyrimidinyl, isoxazolyl, oxaxolyl, indolyl,

benzo[*b*]thienyl, isobenzofuranyl, purinyl, isoquinolyl, pterdinyl, perimidinyl, imidazolyl, pyridyl, pyrazolyl, pyrazinyl, quinolyl, etc.).

"Heteroarylene" means an aromatic monocyclic or fused bicyclic divalent radical containing 5 to 10 annular atoms, wherein each ring contained therein is comprised of 5 to 6 annular members and one or more of the annular atoms is a heteroatom moiety selected from -N=, -NR^9-, -O- or -S-, (e.g., heteroaryl includes thienylene, furylene, pyrrolylene, pyrimidinylene, isoxazolylene, oxaxolylene, indolylene, benzo[*b*]thienylene, isobenzofuranylene, purinylene, isoquinolylene, imidazolylene, pyridylene, pyrazolylene, pyrazinylene, quinolylene, etc.).

"Heterocycloalkyl" means cycloalkyl, as defined above, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety, as defined in this Section, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term heterocyclo(C_{5-14})alkyl includes piperidyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, quinuclidinyl, morpholinyl, etc.).

"Heterocycloalkylene" means cycloalkylene, as defined above, except one or more of the annular carbon atoms indicated is replaced by a heteroatom moiety, as defined in this Section, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term heterocyclo(C_{3-14})alkylene includes piperidylene, pyrrolidinylene, pyrrolinylene,

imidazolidinylene, quinuclidinylene, morpholinylene, etc.).

"Heteropolycycloaryl" means polycycloaryl, as defined in this Section, except one or more of the annular carbon atoms indicated are replaced by a heteroatom moiety, as set defined in this Section, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., heteropolycyclo(C_{8-10})alkyl includes 3,4-dihydro-2*H*-quinolinyl, 5,6,7,8-tetrahydroquinolinyl, 3,4-dihydro-2*H*-[1,8]naphthyridinyl, 2,4-dioxo-3,4-dihydro-2*H*-quinazolinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, etc.).

"Heteropolycycloarylene" means polycycloarylene, as defined in this Section, except one or more of the annular carbon atoms indicated is replaced by a heteroatom moiety, as set defined in this Section, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., heteropolycyclo(C_{8-10})alkylene includes 3,4-dihydro-2*H*-quinolinylene, 5,6,7,8-tetrahydroquinolinylene, 3,4-dihydro-2*H*-[1,8]naphthyridinylene,

2,4-dioxo-3,4-dihydro-2*H*-quinazolinylene, 3-oxo-2,3-dihydrobenzo[1,4]oxazinylene, etc.).

"Hydroxy" means the radical -OH.

"Imino" means the radical =NH.

"Iminoketone derivative" refers to a radical containing the moiety -C(NR)-, wherein R is hydrogen or (C_{1-6})alkyl.

"Isomers" mean compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "steroisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2^{n-1} enantiomeric pairs, where n is the number of chiral centers. Compounds with more than one chiral center may exist as ether an individual diasteromer or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute configuration of

that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 3rd edition, March, Jerry, John Wiley & Sons, New York, 1985). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers. Thus, for example, the name 2-[6-fluoro-4-(5-oxopyrrolidin-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine is meant to include (*S*)-2-[6-fluoro-4-(5-oxopyrrolidin-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine and (*R*)-2-[6-fluoro-4-(5-oxopyrrolidin-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine and any mixture, racemic or otherwise, thereof.

"Ketone derivative" refers to a radical containing the moiety –C(O)–.

"Leaving group" has the meaning conventionally associated with it in synthetic organic chemistry, i.e., an atom or group displaceable under alkylating conditions, and includes, halogen, hydroxy, alkyloxy, alkylsulfonloxy (e.g., mesyloxy, ethanesulfonyloxy, etc.), arylsulfonyloxy (e.g., benzenesulfonyloxy and tosyloxy, thienyloxy), dihalophosphinoyloxy, tetrahalophosphaoxy, and the like.

"Linking group" means a saturated or unsaturated divalent radical having the number of contiguous linking atoms indicated, wherein "contiguous linking atoms" refers to the minimum number of connecting atoms linking the free valences, and any substituted, ketone, thioketone or iminoketone derivative thereof. The linking group may contain one or more heteroatom moieties, as defined in this Section, one or more suitable combinations of heteroatom moieties (e.g., $-OS(O)_2-$, $-S(O)_2O-$, $-N(R^9)S(O)_2-$, $-S(O)_2NR^9-$, $-OP(O)(OR^9)O-$, etc.), alkylene, heteroalkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, polycycloarylene, heteropolycycloarylene, and any combination and carbocyclic ketone, thioketone and iminoketone derivative thereof (e.g., –C(O)–, –C(O)O–, –OC(O)–, $-N(R^9)C(O)-$, $-C(O)NR^9-$, $-N(R^9)C(O)O-$, $-OC(O)NR^9-$, $-N(R^9)C(O)NR^9-$,

-N(R^9)C(N)-, etc.). Hence, a linking group containing 1 to 12 contiguous linking atoms may include one or more heteroatom moieties, one or more suitable combinations of heteroatom moieties and one or more groups selected from (C_{2-10})alkylene, hetero(C_{2-10})alkylene, cycloalkylene, heterocycloalkylene, arylene, heteroarylene, polycycloarylene and heteropolycycloarylene, and any combination thereof (e.g., methylenephen-1,4-ylene (-$C_6H_4CH_2$- or -$CH_2C_6H_4$-), methylenepiperazin-1,4-ylene (-$N_2C_4H_8CH_2$- or -$CH_2N_2C_4H_8$-), methyleneoxaphen-1,4-ylene (-$OC_6H_4CH_2$- or -$CH_2C_6H_4O$-), etc.).

"Mercapto" means the radical -SH.

"Nitro" means the radical -NO_2.

"Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "optionally are substituted with one to three radicals" means that the group referred to may or may not be substituted in order to fall within the scope of the invention.

"*N*-oxide derivatives" means a derivatives of compound of Formula I in which nitrogens are in an oxidized state (i.e., O←N) and which possess the desired pharmacological activity.

"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

"Pharmaceutically acceptable" means that which is userul in preparing a pharmaceutical composition that is generall safe, non-toxic and neither biologically nor otherwise undesirabale and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Perhalo(C_{1-3})alkyl" means alkyl, as defined above, except all of the hydrogen atoms are replaced by haloatoms (e.g., trifluoromethyl, etc.).

"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired pharmacological activity. Such salts include acid addition salts formed with inorganic acids

such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid, benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, madelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic aicd, 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydoxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Polycycloaryl" means a fused polycyclic radical containing the number of annular carbon

atoms indicated, wherein at least one, but not all, of the fused rings comprising the radical is aromatic and each ring contained therein is comprised of 5 to 6 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., polycyclo(C_{9-10})aryl includes indanyl, indenyl, 1,2,3,4-tetrahydronaphthalenyl, 1,2-dihydronaphthalenyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthalenyl, etc.).

"Polycycloarylene" means a fused polycyclic divalent radical containing 10 to 12 annular atoms, wherein at least one, but not both, of the fused rings comprising the radical is aromatic and each ring contained therein is comprised of 5 to 6 annular members, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., polycyclo(C_{9-10})arylene includes indanylene, indenylene,

1,2,3,4-tetrahydronaphthalenylene, 1,2-dihydronaphthalenylene, 2,4-dioxo-1,2,3,4-tetrahydronaphthalenylene, etc.).

"Prodrug derivatives" means derivatives of compounds of Formula I which are converted *in vivo* to the corresponding non-derivatized form of a compound of Formula I. For example, suitable prodrug derivatives include compounds of Formula I wherein the R^1 amidino group is hydroxy- or (C_{1-6})alkyloxy-substituted.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protective groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active inhibitors of factor Xa. For example, a compound of Formula I may have one or more reactive amino groups. Suitable protecting groups for reactive nitrogen atoms include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl and any other suitable amino protective groups (e.g., see T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981).

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" refers to a radical containing the moiety –C(S)–.

"Treatment" or "treating" refers to any administration of a compound of the present invention and includes:

(1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

(2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or

(3) amelorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

"Sulfo" means the radical –S(O)OH.

"Uriedo" means the radical $-NHC(O)NH_2$.

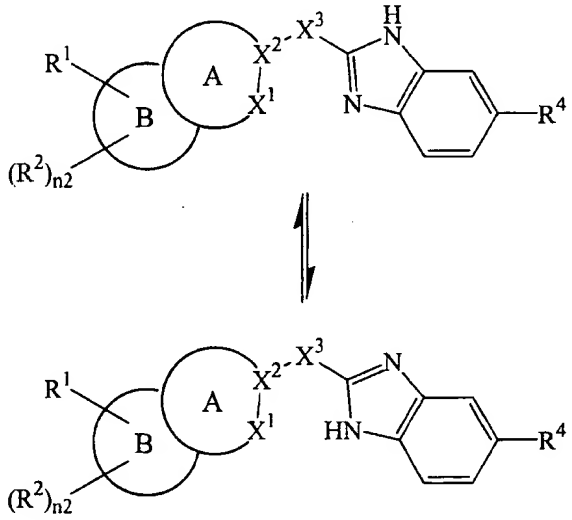
The compounds of Formula I and the intermediates and starting materials used in

their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides and amidines. For example, a compound of Formula I in which:

A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl, C comprises 6-fluoro-4-[2-(2-oxoimidazolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$ is named 2-{6-fluoro-4-[2-(2-oxoimidazolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine; and

A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl, C comprises 5-(2-methoxy)acetylamino-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$ is named *N*-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-2-methoxyacetamide.

Certain compounds of Formula I exist in tautomeric equilibrium. For example, compounds of Formula I in which C comprises 1*H*-benzoimidazol-2-yl exist in equilibrium between tautomers of the following formulae:



wherein R^4 is not hydrogen. Compounds of Formula I which exist as tautomers are named, illustrated or otherwise described in this Application as one possible tautomer. However, it is to be understood that all possible tautomers are meant to be encompassed by such names, illustrations and descriptions. Thus, the name *N*-[2-(5-amidino-

1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-2-methoxyacetamide is meant to include its tautomers *N*-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-3*H*-benzoimidazol-5-ylmethyl]-2-methoxyacetamide, *N*-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)-3*H*-benzoimidazol-5-ylmethyl]-2-methoxyacetamide and *N*-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-2-methoxyacetamide.

Presently Preferred Embodiments:

While the broadest definition of this Invention is set forth in the Summary of the Invention, certain aspects of the Invention are preferred. A preferred aspect of the Invention is a compound of Formula I in which:

n2 is 1;

A together with B comprises a fused heterobicyclic radical containing 8 to 10 annular atoms, wherein each ring contains 5 to 6 annular members;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing from 5 to 18

annular atoms, wherein each ring contains 5 to 6 annular atoms;

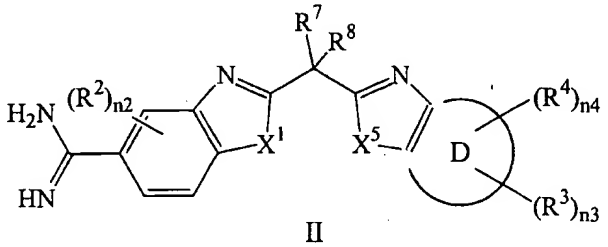
X^3 is -C(O)-, $-NR^7-$ or $-CR^7R^8-$;

R^2 is hydrogen, (C_{1-3})alkyl or halo;

each R^3 is independently hydrogen, cyano, halo, nitro or perhalo(C_{1-3})alkyl; and

each R^4, R^5 and R^8 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 10 contiguous linking atoms and R^6 is hydrogen, (C_{6-10})aryl, cyclo(C_{3-6})alkyl, hetero(C_{5-10})aryl, heterocyclo(C_{5-6})alkyl or hetero(C_{8-10})polycycloaryl.

A further preferred aspect of the Invention is a compound of Formula II:



II

in which D together with the vinylene moiety to which it is fused comprises a monocyclic or heteromonocyclic divalent radical containing 6 annular atoms; and X^1 and X^5 are independently a heteroatom moiety selected from $-NR^5-$, $-O-$ and $-S-$.

A further preferred aspect of the Invention is a compound of Formula II in which each R^4, R^5 and/or R^8 is independently $-R^6$, wherein R^6 is (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl, or $-X^6-R^6$, wherein X^6 is (C_{1-10})alkylene or (C_{2-10})heteroalkylene and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl.

A further preferred aspect of the Invention is a compound of Formula II in which each R^3 is independently cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and/or each R^4 is independently hydroxy, mercapto, sulfo, $-NHR^9$ or $-OP(O)(OR^9)OH$, wherein R^9 is hydrogen or (C_{1-6})alkyl.

A further preferred aspect of the Invention is a compound of Formula II in which one of X^1 and X^5 is $-NR^5-$ and the other is a heteroatom selected from $-O-$ and $-S-$; in particular, compounds

of Formula II wherein X^1 is $-S-$ and X^5 is $-NR^5-$.

A further preferred aspect of the Invention are the following compounds:

2-{4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(2-hydroxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-(5-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[5-(2-amino-2,3-dihydroimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(2,5-dioxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-oxoimidazolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-(4-benzo[1,3]dioxol-5-ylmethoxy-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

(*S*)-2-[6-fluoro-4-(5-oxopyrrolidin-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-(4,6-diimidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(1-azabicyclo[2.2.2]oct-3-yloxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-(6-fluoro-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-{7'-[2-(2-oxopyrrolidin-1-yl)ethoxy]-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-isopropylimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-methylimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(2-dimethylaminoethoxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-(6-ethoxy-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-(6-fluoro-4-tetrahydropyran-2-ylmethoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-oxooxazolidin-3-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(3,3-dimethyl-2-oxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(1,3-dioxooctahydroisoindol-2-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(1-methylpyrrolidin-2-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(2-morpholin-4-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{1-[2-(3,5-dimethyl-2,3-dihydroisoxazole-4-sulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[1-(2-benzylsulfonylaminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{1-[2-(naphthalen-2-ylsulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-(7'-ethoxy-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-[6-chloro-4-(2-piperidin-1-ylethylsulfamoyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine; and

N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-6-fluoro-1*H*-benzoimidazol-4-yloxy]ethyl}acetamide.

Pharmacology and Utility:

The compounds of this invention are factor Xa inhibitors and, as such, are useful for treating diseases in which factor Xa activity contributes to the pathology and/or symptomatology of the disease. Uses for factor Xa inhibitors include therapy in treating venous thromboembolism (obstruction of a blood vessel with thrombotic material carried by the blood stream from the site of origin to plug another vessel), to reduce the risk of myocardial infarction in patients with unstable angina, to ameliorate further loss of cardiac function in patients with acute myocardial infarction, to reduce the risk of occlusion of saphenous grafts, to reduce periprocedural thrombosis in patients undergoing angioplasty procedures, to reduce the risk of ischemic stroke in patients with atrial fibrillation, to reduce the risk of embolism associated with mechanical heart valves and valvular heart disease, to prevent ischemic strokes in patients with cerebrovascular atherosclerosis, in patients with peripheral vascular disease, and the like.

Suitable *in vitro* assays for measuring factor Xa activity and the inhibition thereof by test compounds are known. Typically, the assay measures factor Xa induced hydrolysis of a peptide base substrate. Suitable *in vivo* and *ex vivo* models for measuring the anti-coagulation activity of test compounds are known to those of ordinary skill in the art. For further details of the assays for measuring factor Xa inhibitor and/or anticoagulant activity see Examples 18, 19 and 20, infra.

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly or in combination with another therapeutic agent. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I for anticoagulant therapy may range from 0.1 micrograms per kilogram body weight (μg/kg) per day to 1 milligram per kilogram body weight (mg/kg) per day, typically 1 μg/kg/day to 0.1 mg/kg/day. Therefore, a therapeutically effective amount for a 80 kg human patient may range from 10 μg/day to 10 mg/day, typically 0.1 mg/day to 10 mg/day. In general, one of ordinary skill in the art,

acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective amount of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

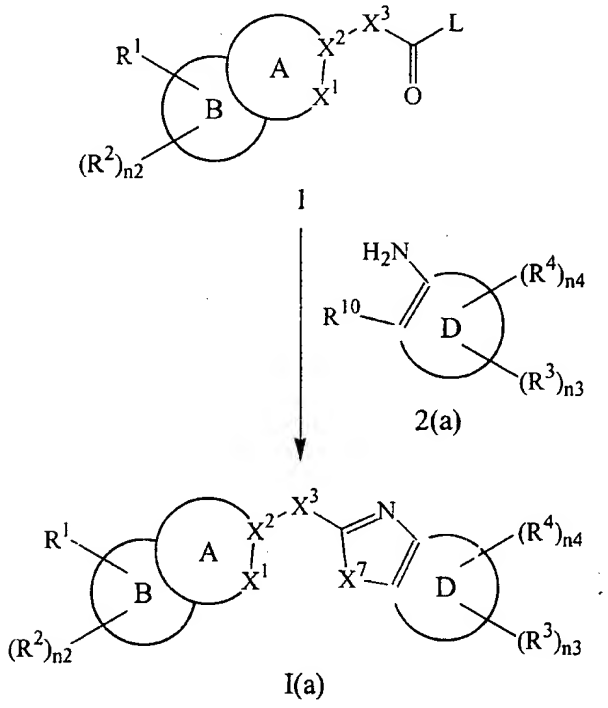
Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g., peanut oil, soybean oil, mineral oil, sesame oil, etc.). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative pharmaceutical formulations containing a compound of Formula I are described in Example 21.

Chemistry:

Compounds of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring and C comprises a fused heteropolycyclic radical can be prepared by the methods depicted in the following reaction scheme:

Scheme 1

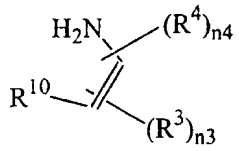


I(a)

in which L is a leaving group, D together with the vinylene moiety to which it is fused comprises a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and optionally one or more annular members is a heteroatom moiety, X^7 is -O-, -N(R^5)- or -S-, R^{10} is -OH, -NHR^5 or -SH and heteroatom moiety, n2, n3, n4, A, B, X^1, X^2, X^3, R^1, R^2, R^3, R^4 and R^5 are as defined in the Summary of the Invention.

Compounds of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring comprising a fused heteropolycyclic radical

(Formula I(a)) can be prepared by reacting a compound of Formula 1 with a compound of Formula 2(a). The reaction may be carried out neat, but preferably is carried out in the presence of 1,3-dimethyl-3,4,5,6-tetrahydro-2(1*H*)-pyrimidinone (DMPU) or polyphosphoric acid, at 160 to 200 °C, preferably 170-180 °C, and requires 2 to 3 hours to complete (e.g., see Examples 10 and 11, infra.). Compounds of Formula I in which C comprises 1*H*-imdazol-2-yl, thiazol-2-yl or oxazol-2-yl can be prepared by proceeding as in Scheme I, but replacing the compound of Formula 2(a) with a compound of Formula 2(b):

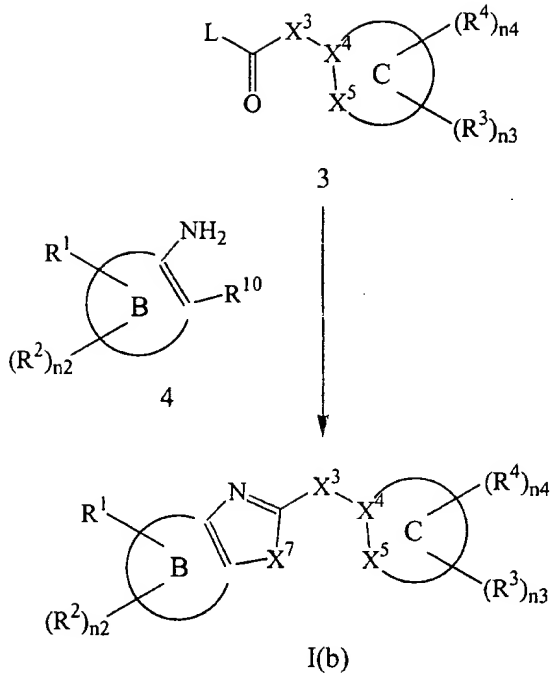


2(b)

in which R^{10} is -OH, -NHR^5 or -SH and each q, R^3, R^4 and R^5 is as defined in the Summary of the Invention.

In a similar fashion, compounds of Formula I in which X^1 and X^2 adjacent members of a oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring can be prepared by the methods depicted in the following reaction scheme:

Scheme 2



3

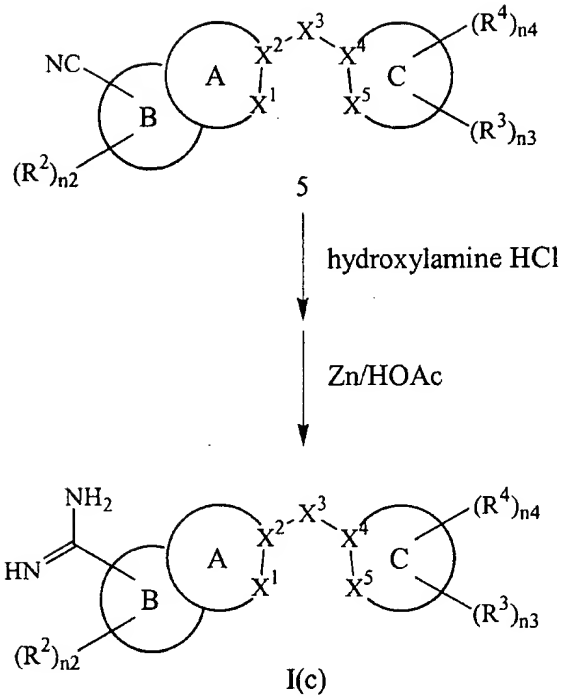
4

I(b)

in which L is a leaving group, X^7 is -O-, -N(R^5)- or -S-, R^{10} is -OH, -NHR^5 or -SH and n2, n3, n4, B, C, X^3, X^4, X^5, R^1, R^2, R^3, R^4 and R^5 are as defined in the Summary of the Invention.

Compounds of Formula I can be prepared by the methods depicted in the following reaction scheme:

Scheme 3



I(c)

in which n2, n3, n4, A, B, C, X^1, X^2, X^3, X^4, X^5, R^2, R^3 and R^4 are as defined in the Summary of the Invention.

Compounds of Formula I can be prepared by reacting a corresponding nitrile with hydroxylamine hydrochloride to give a *N*-hydroxycarboxamidine and then dehydroxylating to give the unsubstituted carboxamidine. The reaction with the hydroxylamine may be carried out in the presence of sodium bicarbonate and in a suitable solvent (e.g., ethanol) at reflux temperature and requires 12 to 18 hours (see Example 12, infra). The dehydroxylation can be effected by reacting the *N*-hydroxycarboxamidine with zinc in the presence of acetic acid at reflux temperature and requires 3 to 4 hours to complete (see Example 13, infra.).

In general, the starting materials required for preparing the compounds of Formula I are either commercially available or can be readily prepared by methods known to those of ordinary skill in the art or as described herein. For example, compounds of Formula 1 or Formula 3 in which L is ethoxy, X^3 is $-CH_2-$ and X^1 and X^2 or X^4 and X^5 are adjacent members of an imidazole, thiazole or oxazole ring can be prepared by reacting an appropriate compound of Formula 4 or Formula 2, respectively, with ethyl

ethoxycarbonimidoylacetate hydrochloride. The reaction is carried out in the presence of a suitable solvent (e.g., anhydrous ethanol) at 80 °C and typically requires approximately 18 hours to complete (see Example 2, infra.).

Compounds of Formula 2(a) can be prepared by reducing a corresponding 2-nitroaniline. The reduction can be effected with catalytic hydrogenation in the presence of a suitable catalyst (e.g, 10% palladium on carbon) and in a suitable solvent (e.g., methanol, ethanol, acetic acid, etc.) and requires 3 to 24 hours to complete (see Examples 3, 4, 5 and 6, infra.).

Compounds of Formula 2(a) in which R^4 is -OR, -NRR' or -SR, wherein R and R' are independent or together with the nitrogen atom to which they are attached form heterocycloalkyl, can be prepared by reacting a correspondingly appropriate amine, alcohol, thiol or heterocycloalkane with a corresponding halo-subsituted nitroaniline and then reducing. The reaction with the halo-substituted nitroaniline typically is carried out in a suitable solvent (e.g., THF) at 0 to 25 °C and requires 4 to 5 hours to complete (see Example 3, infra.).

Compounds of Formula 2(a) in which R^{10} is $-NHR^5$ can be prepared by reacting a correspondingly appropriate amine of the formula NH_2R^5 with a corresponding 1-halo-2-nitrobenzene and then reducing. The reaction with the 1-halo-2-nitrobenzene typically is carried out in a suitable solvent (e.g., dimethyl sulfoxide) at 0 to 25 °C and requires 4 to 5 hours to complete (see Example 4, infra.).

Additional Processes for Preparing Compounds of Formula I:

Compounds of Formula I in which R^4, R^5 or R^8 comprises $-X^8C(O)NR^9X^9R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^8 comprises $-X^8C(O)OH$ with a compound having the formula $R^6X^9NHR^9$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of 1-hydroxybenzotriazole (HOBT) and a coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidinophosphonium hexafluorophosphate (PyBOP),

1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (EDCI), 1,1-carbonyldiimidazole, etc.) and a non-nucleophillic base (e.g., *N*-methylmorpholine, *N,N*-diisopropylethylamine, etc.) and in a suitable solvent (e.g., *N,N*-dimethylformamide (DMF), tetrahydrofuran (THF), dichloromethane, etc., preferably DMF) at 20 to 25 °C and requires 12 to 24 hours to complete.

Compounds of Formula I in which R^4, R^5 or R^8 comprises $-X^8NR^9C(O)X^9R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^8 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9C(O)OH$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of a coupling agent (e.g., PyBOP, EDCI, 1,1-carbonyldiimidazole, etc.) and a non-nucleophillic base (e.g., *N*-methylmorpholine, *N,N*-diisopropylethylamine, etc.) and in a suitable solvent (e.g., DMF, THF, dichloromethane, etc., preferably DMF) at 20 to 25 °C and requires 6 to 24 hours to complete (see Example 14, infra.).

Compounds of Formula I in which R^4, R^5 or R^8 comprises $-X^8NR^9S(O)_2X^9R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^8 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9S(O)_2Cl$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of a non-nucleophillic base (e.g., *N*-methylmorpholine, *N,N*-diisopropylethylamine, etc.) and in a suitable solvent (e.g., DMF, THF, dichloromethane, etc., preferably DMF) at 20 to 25 °C and requires 12 to 24 hours to complete (see Example 15, infra.).

Compounds of Formula I in which R^4, R^5 or R^8 comprises $-X^8NR^9CH_2X^9R^6$ can be prepared by reacting a corresponding compound of Formula I in which R^4, R^5 or R^8 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9C(O)H$ under reducing conditions, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention. The reaction typically is carried out in the presence of a reducing agent (e.g., sodium cyanoborohydride) and in a suitable

solvent (e.g., methanol) at 20 to 25 °C and requires 12 to 24 hours to complete (see Example 16, infra.).

Compounds of Formula I may be prepared as pharmaceutically acceptable acid addition salts by reacting the free base forms of a compound of Formula I with a pharmaceutically acceptable inorganic or organic acid. Alternatively, the pharmaceutically acceptable base addition salts of compounds of Formula I may be prepared by reacting the free acid forms of compounds of Formula I with pharmaceutically acceptable inorganic or organic bases. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of Formula I may be prepared using salts of the starting materials or intermediates.

The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, compounds of Formula I in an acid addition salt form may be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, etc.). Compounds of Formula I in a base addition salt form may be converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g., trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenozic acid, etc.) in a suitable inert organic solvent (e.g., a halogenated such as methylene chloride) at approximately 0 °C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide, triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, etc.) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, etc.) at 0 to 80 °C.

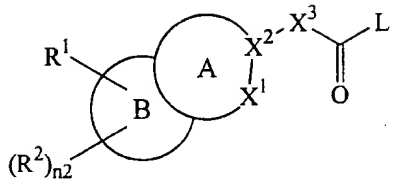
Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.*(1994), *Bioorganic and Medicinal Chemistry Letters*. 4:1985).

Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protective groups and their removal can be found in T.W. Greene, *Protective Groups in Organic Synthesis*, John Wiley & Sons, Inc. 1981.

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair of diastereomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of compounds from their racemic mixtures can be found in Jean Jacques, Andre Collet, Samuel H. Wilen, Enantiomers, Racemates and Resolutions, John Wiley & Sons, Inc. (1981).

In summary, an aspect of this Invention is a process for preparing a compound of Formula I, which process comprises:

(a) reacting a compound of Formula 1:



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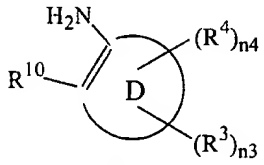
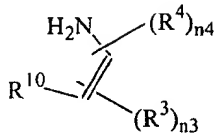
with a compound of Formula 2(a) or 2(b):



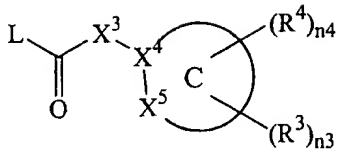
2(a)



2(b)

in which L is a leaving group, D together with the vinylene moiety to which it is fused comprises a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and optionally one or more annular members is a heteroatom moiety, R^{10} is -OH, -NHR^5 or -SH and heteroatom moiety, n2, n3, n4, A, B, X^1, X^2, X^3, R^1, R^2, R^3, R^5 and R^4 are as defined in the Summary of the Invention, to give a compound of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(b) reacting a compound of Formula 3:



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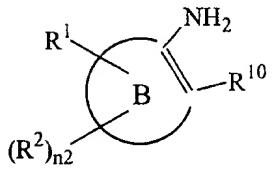
with a compound of Formula 4:



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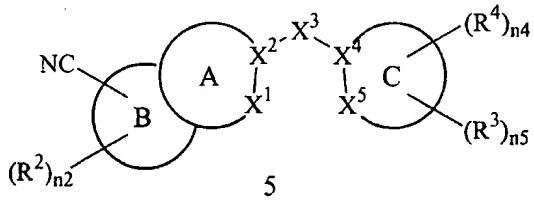
in which L is a leaving group, R^{10} is -OH, $-NHR^5$ or -SH and n2, n3, n4, B, C, X^3, X^4, X^5, R^1, R^2, R^3, R^4 and R^5 are as defined in the Summary of the Invention, to give a compound of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(c) reacting a compound of Formula 5:



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in which n2, n3, n4, A, B, C, X^1, X^2, X^3, X^4, X^5, R^2, R^3 and R^4 are as defined in the Summary of the Invention with hydroxylamine hydrochloride to give a corresponding *N*-hydroxycarboxamidine and then dehydroxylating;

(d) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8C(O)OH$ with a compound having the formula $R^6X^9NHR^9$ to give a compound of Formula I in which R^4 or R^5 comprises $-X^8C(O)NR^9X^9R^6$, wherein X^8 and X^9 are linking

groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(e) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9C(O)OH$ to give a compound of Formula I in which R^4 or R^5 comprises $-X^8NR^9C(O)X^9R^6$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(f) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9S(O)_2Cl$ to give a compound of Formula I in which R^4 or R^5 comprises $-X^8NR^9S(O)_2X^9R^6$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(g) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9C(O)H$ under reducing conditions to give a compound of Formula I in which R^4 or R^5 comprises $-X^8NR^9CH_2X^9R^6$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined in the Summary of the Invention;

(h) optionally further converting a compound of Formula I into a pharmaceutically acceptable salt;

(i) optionally further converting a salt form of a compound of Formula I to non-salt form;

(j) optionally further converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(k) optionally further an *N*-oxide form of a compound of Formula I its unoxidized form;

(l) optionally further converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(m) optionally further converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

Examples:

EXAMPLE 1

Ethyl ethoxycarbonimidoylacetate

A mixture comprising ethyl cyanoacetate (200 mL, 188.14 g, 1.67 mol), toluene (1 L) and anhydrous ethanol (175 mL) in a 2 L three-neck flask, equipped with a drying tube, was cooled to 0 °C and sparged with hydrogen chloride gas for 1 hour. The reaction flask was sealed and the mixture was allowed to warm to ambient temperature, stirred for 18 hours and diluted with anhydrous diethyl ether (2 L) to give a precipitate. The precipitate was collected and washed with anhydrous diethyl ether to provide ethyl ethoxycarbonimidoylacetate hydrochloride (270 g, 1.38 mmol) as a white crystalline solid, ^{1}H NMR (300 MHz, D_6-DMSO): δ 1.16 (t, 3H, J = 7.1), 1.30 (t, 3H, J = 7.1), 3.98 (s, 2H), 4.11 (q, 2H, J = 7.1), 4.50 (q, 2H, J = 7.1), 7.50 (bs, 1H), 7.69 (bs, 1H); ^{13}C NMR (75 MHz, D_6-DMSO): δ 13.43, 13.95, 60.53, 61.81, 70.02, 165.36, 172.41; Electrospray MS ($M+H^+$).

EXAMPLE 2

Ethyl (5-amidino-1*H*-benzoimidazol-2-yl)acetate,
a compound of Formula 1 in which L is ethoxy, A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture comprising 3,4-diaminobenzamidine hydrochloride (33 g, 177 mmol), ethyl ethoxycarbonimidoylacetate hydrochloride (39.8 g, 203 mmol) and anhydrous ethanol (200 mL) was stirred for 18 hours at 80 °C. The mixture was allowed to cool to ambient temperature, filtered, concentrated to saturation and added dropwise to vigorously stirring anhydrous acetonitrile (2 L) to give a precipitate. The precipitate was collected and dried under vacuum to provide ethyl

(5-amidino-1*H*-benzoimidazol-2-yl)acetate hydrochloride (45 g, 159 mmol) as a tan solid, ^{1}H NMR (300 MHz, D_6-DMSO): δ_1.18 (t, 3H, *J* = 7.2), 4.06 (s, 2H), 4.12 (q, 2H, *J* = 7.2), 7.69 (m, 2H), 8.14 (s, 1H), 9.22 (bs, 2H), 9.42 (bs, 2H); ^{13}C NMR (75 MHz, D_6-DMSO): δ 14.07, 35.13, 61.00, 120.80, 121.62, 151.34, 166.21, 168.43; Electrospray MS 246.8 ($M+H^+$).

EXAMPLE 3

5-Fluoro-3-(1*H*-imidazol-1-yl)benzene-1,2-diamine,

a compound of Formula 2(a) in which D together with the vinylene moiety to which it is fused comprises 5-fluoro-3-(1*H*-imidazol-1-yl)-1,2-phenylene and R^{10} is amino

A mixture comprising 1,3,5-trifluoro-2-nitrobenzene (15 g, 85 mmol) and 0.5N ammonia in 1,4-dioxane (425 mL) in a sealed flask was stirred for 72 hours at ambient temperature and then poured into 5 L of vigorously stirring water to give a precipitate. The precipitate was collected to give 2,4-difluoro-6-nitroaniline (11 g, 64 mmol), ^{1}H NMR (300 MHz, D_6-DMSO): δ 6.47-6.56 (m, 2H), 7.34 (bs, 2H); ^{13}C NMR (75 MHz, D_6-DMSO): δ 92.43 (dd, *J* = 29.1, 25.9), 98.83 (dd, *J* = 25.9, 3.6), 120.71 (d, *J* = 9.3), 147.90 (dd, *J* = 16.1, 1.6), 158.12 (dd, *J* = 258.5, 17.6), 164.25 (dd, *J* = 250.7, 17.1); EI MS 175 ($M+H^+$).

A mixture comprising 1*H*-imidazole (3 g, 44 mmol), anhydrous THF (100 mL) and sodium *tert*-butoxide (2.65 g, 27.5 mmol) was cooled to 0 °C and then 2,4-difluoro-6-nitroaniline (3.84 g, 22 mmol) was added in a single portion. The reaction mixture was stirred for 30 minutes at 0 °C and then 4 hours at ambient temperature, diluted with water (100 mL) and saturated aqueous $NaHCO_3$ solution (100 mL) and extracted with ethyl acetate (2x 150 mL). The combined organic layers were dried ($MgSO_4$) and concentrated to dryness. The residue was purified by silica gel flash chromatography using 5% methanol in dichloromethane as eluents to provide 4-fluoro-2-(1*H*-imidazol-1-yl)-6-nitroaniline (3.5 g, 15.8 mmol) as orange crystals.

A mixture comprising 4-fluoro-2-(1*H*-imidazol-1-yl)-6-nitroaniline (2 g, 9 mmol), palladium hydroxide on carbon (Pearlman's catalyst, 100 mg) and ethanol (100 mL) was hydrogenated for 3 hours. The mixture was filtered and concentrated to provide 5-fluoro-3-(1*H*-imidazol-1-yl)benzene-1,2-diamine (1.64 g, 8.6 mmol) as a white waxy solid, ^{1}H NMR (300

MHz, D_6-DMSO): δ 5.01 (s, 2H), 7.61 (dd, 1H, J = 8.7, 2.2), 7.78 (dd, 1H, J = 10.4, 2.2), 7.90 (dd, 1H, J = 8.7, 1.5), 7.94-7.98 (m, 2H), 8.34 (s, 1H), 8.57 (t, 1H, J = 1.7), 9.42 (bs, 2H), 9.69 (bs, 2H), 10.15 (t, 1H, J = 1.5); ^{13}C NMR (75 MHz, D_6-DMSO): δ 27.81, 101.86 (dd, J = 274.15, 30.6), 114.69, 115.48, 120.25, 121.57, 123.96 (t, J = 6.7), 124.43, 131.27, 132.98, 135.87, 136.38 (d, J = 6.7), 136.66, 150.48, 151.97, 156.25, 159.75, 165.55; Plasma TOF MS 375.8 ($M+H^+$).

Proceeding as in Example 3, but substituting other starting materials, provided the following compounds of Formula 2(a):

5-fluoro-3-(2-methyl-1*H*-imidazol-1-yl)benzene-1,2-diamine, 5-fluoro-3-(4-methyl-1*H*-imidazol-1-yl)benzene-1,2-diamine, 5-fluoro-3-(2-isopropyl-1*H*-imidazol-1-yl)benzene-1,2-diamine, 5-fluoro-3-tetrahydrofuran-2-ylmethoxybenzene-1,2-diamine, 1-[2-(2,3-diamino-5-fluorophenoxy)ethyl]pyrrolidin-2-one, 1-[2-(2,3-diamino-5-fluorophenoxy)ethyl]pyrrolidine-2,5-dione, 2-[2-(2,3-diamino-5-fluorophenoxy)ethyl]-3a,4,7,7a-tetrahydroisoindole-1,3-dione, 5-fluoro-3-phenoxybenzene-1,2-diamine, 5-fluoro-3-(2-pyrrolidin-1-ylethoxy)benzene-1,2-diamine, 3-(2-dimethylaminoethoxy)-5-fluorobenzene-1,2-diamine, 5-fluoro-*N*-(2-imidazol-1-ylethyl)benzene-1,2,3-triamine, 5-fluoro-*N*-(2-pyridin-2-ylethyl)benzene-1,2,3-triamine, 5-fluoro-3-(tetrahydropyran-2-ylmethoxy)benzene-1,2-diamine, 5-fluoro-3-[2-(4-methylthiazol-5-yl)ethoxy]benzene-1,2-diamine, 3-[2-(2,3-diamino-5-fluorophenoxy)ethyl]oxazolidin-2-one, 1-[2-(2,3-diamino-5-fluorophenoxy)ethyl]-3,3-dimethylpyrrolidin-2-one, 2-[2-(2,3-diamino-5-fluorophenoxy)ethyl]hexahydroisoindole-1,3-dione, 5-fluoro-3-[2-(1-methylpyrrolidin-2-yl)ethoxy]benzene-1,2-diamine, 5-fluoro-N^1-methyl-3-tetrahydrofuran-2-ylmethoxybenzene-1,2-diamine and 5-fluoro-3-[2-(2-methoxyethoxy)ethoxy]-N^1-methylbenzene-1,2-diamine.

EXAMPLE 4

N-[2-(2-Aminophenylamino)ethyl]acetamide,

a compound of Formula 2(a) in which D together with the vinylene moiety to which it is fused comprises 1,2-phenylene and R^{10} is $-NHR^5$, wherein R^5 is 2-acetylaminoethyl

A solution comprising *N*-(2-aminoethyl)acetamide (11.8 g, 116 mmol) in anhydrous dimethyl sulfoxide (10 mL) was cooled to 0 °C and 1-fluoro-2-nitrobenzene (3.73 mL, 35 mmol) was added dropwise. The mixture was stirred 4 hours at ambient temperature, quenched with brine (200 mL) and cooled to 0 °C to give a precipitate. The precipitate was collected by filtration , washed with 1N hydrochloric acid and dried *in vacuo* to provide *N*-[2-(2-nitrophenylamino)ethyl]acetamide (7.81 g, 34.8 mmol). A suspension comprising *N*-[2-(2-nitrophenylamino)ethyl]acetamide (2.0 g, 8.9 mmol), 10% palladium on carbon (200 mg) and methanol (200 mL) was hydrogenated for 18 hours, filtered and concentrated to provide *N*-[2-(2-aminophenylamino)ethyl]acetamide (1.56 g, 8.01) as a brown oil.

Proceeding as in Example 4, but substituting other starting materials, provided the following compounds of Formula 2(a):

N-butylbenzene-1,2-diamine, *N*-phenylbenzene-1,2-diamine, *N*-(3-phenylpropyl)benzene-1,2-diamine, 4-(2-aminophenylamino)phenol, 4-chloro-N^2-phenylbenzene-1,2-diamine, 2-[2-(2-aminophenylamino)ethyl]isoindole-1,3-dione, 2-(2-aminophenylamino)ethanol, *N*-[2-(2-aminophenylamino)ethyl]acetamidine, *N*-[2-(2-aminophenylamino)ethyl]succinamic acid, *N*-[2-(2-aminophenylamino)ethyl]-3-piperidin-1-ylpropionamide and *N*-[2-(2-aminophenylamino)ethyl]hexanamide.

EXAMPLE 5

N-(3,4-Diaminobenzyl)acetamide,

a compound of Formula 2(a) in which D together with the vinylene moiety to which it is fused comprises 5-acetylaminomethyl-1,2-phenylene and R^{10} is amino

Borane-THF complex (100 mL of a 1M solution in THF, 2.0 eq.) was added dropwise to a solution of 4-amino-3-nitrobenzonitrile (8.16 g, 50 mmol) in anhydrous THF (100 mL) under a nitrogen atmosphere. The mixture was heated at reflux for 45 minutes, cooled to ambient temperature, slowly diluted with a solution of 1M hydrogen chloride in dry methanol (110 mL, 2.1 eq) and then concentrated. The residue was dissolved in methanol and the solution concentrated (3X) to provide 4-aminomethyl-2-nitrophenylamine hydrochloride as an orange solid.

The 4-amino-3-nitrobenzylamine hydrochloride (9.16 g, 45 mmol) was dissolve in methanol (250 mL) and then acetic anhydride (9.19 g, 8.5 mL, 90 mmol, 2 equiv) and 1 M sodium hydroxide (180 mL, 4 equiv) were sequentially added to the solution. The mixture was stirred for 18 hours and then 1 M sodium hydroxide (45 mL, 1 eq) and acetic anyhydride (4.3 mL, 1 eq) was added. The reaction was allowed to proceed 20 minutes and then the mixture was concentrated by roto-evaporation. The residue was dissolved in ethyl acetate and the solution was washed with 1M $NaHSO_4$ and then brine, dried ($MgSO_4$) and concentrated to provide *N*-(4-amino-3-nitrobenzyl)acetamide (7.07 g, 34 mmol) as an orange solid. The *N*-(4-amino-3-nitrobenzyl)acetamide (7.07 g, 34 mmol) and 10% palladium on carbon (200 mg) were suspended in acetic acid (200 mL) and the mixture was hydrogenated for 18 hours, filtered and concentrated to provide *N*-(3,4-diaminobenzyl)acetamide (6.3 g, 35.2) as a red oil.

Proceeding as in Example 5, but substituting other starting materials, provided the following compounds of Formula 2(a):

3-cyclohexyl-*N*-(3,4-diaminobenzyl)propionamide,

N-(3,4-diaminobenzyl)-2-(2,5-dioxoimidazolidin-4-yl)acetamide, *N*-(3,4-diaminobenzyl)-

2-methoxyacetamide, *N*-(3,4-diaminobenzyl)-2-phenoxyacetamide, *N*-3,4-diaminobenzyl-

5-methylpyrazine-2-carboxamide, 2-benzo[1,3]dioxol-5-yl-
N-(3,4-diaminobenzyl)acetamide, *N*-(3,4-diaminobenzyl)-
2-(*p*-tolylsulfonylamino)acetamide, *N*-(3,4-diaminobenzyl)-4-trifluoromethoxybenzamide,
4-cyano-*N*-(3,4-diaminobenzyl)benzamide, 3-phenylsulfonyl-
N-(3,4-diaminobenzyl)propionamide, *N*-(3,4-diaminobenzyl)pyridine-2-carboxamide,
N-(3,4-diaminobenzyl)-4-phenylbutyramide, *N*-(3,4-diaminobenzyl)-
2-(pyridin-4-ylsulfanyl)acetamide, *N*-3,4-diaminobenzylhexanamide and
N-(3,4-diaminobenzyl)-3-methoxypropionamide.

EXAMPLE 6

2,5-Diamino-3-nitrobenzenesulfonamide,

a compound of Formula 2(a) in which D together with the vinylene moiety to which it is fused comprises 3-aminosulfonyl-5-chloro-1,2-phenylene and R^{10} is amino

2,5-Dichlorobenzenesulfonyl chloride (1.0 g, 4.07 mmol) was dissolved in concentrated H_2SO_4 (5 mL) and fuming HNO_3 (5 mL). The mixture was heated for 18 hours at 80 °C, cooled to ambient temperature and poured over ice (250 mL). The mixture was extracted with ethyl acetate and the extract was dried ($MgSO_4$) and concentrated to an oil. The residue was purified by flash chromatography (10% ethyl acetate:hexanes) to provide 2,5-dichloro-3-nitrobenzenesulfonyl chloride (0.6 g, 51%) as a light yellow oil.

N,N-Diisopropylethylamine (1.2 mL, 6.88 mmole, 2.0 equiv) was added to a solution comprising ammonia (1.1 equiv), 2,5-dichloro-3-nitrobenzenesulfonyl chloride (1.0 g, 3.44 mmol) and ethyl acetate (50 mL) and the mixture was stirred for 30 minutes at ambient temperature. The mixture was diluted with ethyl acetate (200 mL) and the dilution was washed three times with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated to provide 2,5-dichloro-3-nitrobenzenesulfonamide in quantitative yield.

A mixture comprising 2,5-dichloro-3-nitrobenzenesulfonamide (0.7 g, 2.58 mmole) and saturated ammonium hydroxide solution (25 mL) was heated in a sealed tube at 110 °C for 18 hours. The mixture was cooled to ambient temperature, diluted with ethyl acetate

(200 mL), washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated to provide

2-amino-5-chloro-3-nitrobenzenesulfonamide (552 mg, 85 %).

A mixture of 2-amino-5-chloro-3-nitrobenzenesulfonamide (0.5 g, 1.99 mmol, 1.0 eq) $Na_2S_2O_4$ (10 eq), water (50 mL) and THF (30 mL) was stirred in a sealed tube at ambient temperature for 4 hours. The mixture was diluted with 200 mL of ethyl acetate, washed with saturated aqueous $NaHCO_3$ solution, dried ($MgSO_4$) and concentrated to provide 2,5-diamino-3-nitrobenzenesulfonamide in quantative yield.

Proceeding as in Example 6, but substituting other starting materials, provided the following compounds of Formula 2(a):

2,5-diamino-*N*-[2-(2-hydroxyethoxy)ethyl]-3-nitrobenzenesulfonamide;
2,5-diamino-*N*-benzo[1,3]dioxol-5-ylmethyl-3-nitrobenzenesulfonamide;
2-(4-benzylpiperazin-1-ylsulfonyl)-6-nitrobenzene-1,4-diamine; and
2-nitro-6-(2-piperidin-1-ylethylsulfonyl)benzene-1,4-diamine.

EXAMPLE 7

4-Benzoimidazol-1-ylbenzene-1,2-diamine,

a compound of Formula 2(a) in which D together with the vinylene moiety to which it is fused comprises 4-benzoimidazol-1-yl-1,2-phenylene and R^{10} is amino

A mixture comprising 5-chloro-2-nitro-phenylamine (1.46 g, 8.47 mmol, 1.0 eq), benzoimidazole (1.0 g, 8.47 mmol, 1.0 eq), DMPU (4 mL) and sodium *tert*-butoxide (0.95 g, 9.89 mmol, 1.2 eq) was heated at 160 °C for 1 hour, cooled to ambient temperature and diluted with water (100 mL) to give a precipitate. The precipitate was collected and dried to provide an orange solid. The solid was purified by chromatography (Silica) with ethyl acetate to provide 5-benzoimidazol-1-yl-2-nitrophenylamine. A mixture comprising the purified 5-benzoimidazol-1-yl-2-nitrophenylamine, 10% palladium on carbon and methanol (200 mL) was hydrogenated for 18 hours, filtered and concentrated to provide

4-benzoimidazol-1-ylbenzene-1,2-diamine (0.9 g, 47%) as a brown amorphous solid.

Proceeding as in Example 7, but substituting other starting materials, provided the following compounds of Formula 2(a):

4-imidazol-1-ylbenzene-1,2-diamine;
4-[1,2,4]triazol-1-ylbenzene-1,2-diamine;
4-[1,2,3]triazol-1-ylbenzene-1,2-diamine;
4-pyrazol-1-ylbenzene-1,2-diamine; and
4-(2-methylimidazol-1-yl)benzene-1,2-diamine.

EXAMPLE 8

Methyl 8-hydroxyquinolin-2-ylacetate,

a compound of Formula 3 in which L is ethoxy, C comprises 8-hydroxyquinolin-2-yl and X^3 is $-CH_2-$

Methyl 2-(8-hydroxy-4a,8a-dihydro-1*H*-quinolin-2-ylidene)-3-oxo-butyrate (1.87 g, 6.2 mmol) was added over 10 minutes to 10% aqueous hydrochloric acid solution (10 mL). The mixture was made basic with saturated aqueous bicarbonate and extracted with chloroform. The organic phase was separated, dried ($MgSO_4$) and concentrated. The residue was dried *in vacuo* and then dissolved in methanol. The solution was treated with K_2CO_3 at room temperature for 90 min. The mixture was concentrated to dryness and the residue was dissolved in water. The solution was neutralized and extracted with chloroform. The organic phase was separated, dried ($MgSO_4$) and concentrated. The residue was dried *in vacuo* to provide methyl 8-hydroxyquinolin-2-ylacetate (1.21 g, 5.6 mmol) as a yellow oil; ^{1}H NMR d 9.55 (s, 1 H), 8.24 (d, 1 H, J=10 Hz), 7.47 (d, 1 H, J = 10 Hz), 7.31 (m, 3 H), 7.04 (d, 1 H, J = 8 Hz), 6.92 (bs, 1 H), 4.04 (s, 3 H). LRMS (CI) calcd for $C_{12}H_{11}NO_3$ + H 218; found 218.

EXAMPLE 9

3,4-Diaminobenzamidine,

a compound of Formula 4 in which B together with the vinylene moiety to which it is fused comprises 5-amidino-1,2-phenylene and R^{10} is amino

A mixture comprising 4-amino-3-nitrobenzonitrile (50 g, 306 mmol), 1,4-dioxane (500 mL) and anhydrous ethanol (500 mL) in a 2 L three-neck flask, equipped with a drying tube and N_2-inlet, was cooled to 0 °C and sparged with hydrogen chloride gas for 1.5 hours. The reaction flask was sealed and the reaction mixture was allowed to warm to ambient temperature, stirred for 18 hours and then poured into anhydrous diethyl ether to give a precipitate. The precipitate was collected and washed with anhydrous diethyl ether to provide ethyl 4-amino-3-nitrobenzoimidate hydrochoride (67.8 g, 276 mmol) as a yellow solid.

A mixture comprising ethyl 4-amino-3-nitrobenzoimidate hydrochoride (65 g, 266 mmol) and anhydrous ethanol (750 mL) in a 2 L three-neck flask, equipped with a drying tube and N_2-inlet, was cooled to 0 °C and sparged with ammonium gas for 2 hours. The reaction flask was sealed and the reaction mixture was allowed to warm to ambient temperature, stirred for 18 hours and then poured into ether (1 L) to give a precipitate. The precipitate was collected and washed with ether to provide 4-amino-3-nitrobenzamidine hydrochloride (53.3 g, 246 mmol) as a yellow solid, ^{1}H NMR (300 MHz, D_6-DMSO): δ 7.17 (d, 1H, J = 8.9), 7.86 (dd, 1H, J = 9.1, 2.2), 8.17 (bs, 2H), 8.62 (d, 1H, J = 2.2), 9.22 (bs, 4H); ^{13}C NMR (75 MHz, D_6-DMSO): δ 113.29, 119.46, 127.60, 129.62, 133.66, 149.11, 163.49; Electrospray MS ($M+H^+$).

A mixture comprising 4-amino-3-nitrobenzamidine hydrochloride (15 g, 69 mmol), palladium hydroxide on carbon (Pearlman's Catalyst, 1 g) and methanol (200 mL) in a 500 mL Parr hydrogenation flask was hydrogenated (50 psi) for 1.5 hours. The mixture was filtered, concentrated to saturation and then added dropwise to vigorously stirring anhydrous diethyl ether (2 L) to give a precipitate. The precipitate was collected and dried under vacuum to provide 3,4-diaminobenzamidine hydrochloride (12.1 g, 65 mmol) as a tan solid, ^{1}H NMR (300 MHz, D_6-DMSO): δ 4.90 (bs, 2H), 5.69 (bs, 2H), 6.58 (d, 1H, J = 8.2), 6.93 (d, 1H, J = 2.2), 6.99 (dd, 1H, J = 8.16, 2.2), 8.69 (bs, 2H), 8.79 (bs, 2H); ^{13}C NMR (75

MHz, D_6-DMSO): δ 112.57 (2 carbons), 114.00, 118.77, 134.19, 141.67, 165.52; Electrospray MS 150.7 ($M+H^+$).

EXAMPLE 10

2-(5,6-difluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 1),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl, C comprises 5-benzolyl-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture comprising 3,4-diaminobenzamidine (0.78 g, 4.16 mmol, 1 eq), ethyl 5,6-difluoro-1*H*-benzoimidazol-2-ylacetate (1 g, 4.16 mmol, 1 eq) and polyphosphoric acid (5 mL) was heated for 2.5 hours at 165 °C, cooled to 80 °C, diluted with water (15 mL) and then adusted to pH 6 with 50% aqueous sodium hydroxide to give a precipitate. The precipitate was collected, washed with water and dried to provide 2-(5,6-difluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (1.51 g, 91%), MS (ESI), Calculated for $C_{16}H_{12}F_2N_6$: MH^+: 326.31, Found: MH^+: 326.9.

Proceeding as in Example 10, but substituting other starting materials, provided the following compounds of Formula I:

2-(1*H*-imidazol-4-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 2);

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-*N*-(2-naphthalen-1-ylethyl)-1*H*-benzoimidazole-5-carboxamide (Compound 3);

2-(1*H*-benzoimidazol-2-ylcarbonyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 4), MS (BIOION), Calculated for $C_{16}H_{12}N_6O$: MH^+: 304.1, Found: MH^-: 304.8;

2-(1*H*-benzoimidazol-2-ylmethyl)-1-methyl-1*H*-benzoimidazole-5-carboxamidine (Compound 5), MS (ESI), Calculated for $C_{17}H_{16}N_6$: MH^+: 304.36, Found: MH^+: 305.1;

1-allyl-2-(1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 6);

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxylic acid

(Compound 7), MS (BIOION), Calculated for $C_{17}H_{14}N_6O_2$: MH^+: 334.3, Found: MH^+: 335.1;

2-[1-(1*H*-benzoimidazol-2-yl)ethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 8), MS (ESI), Calculated for $C_{17}H_{14}N_6O_2$: MH^+: 334.3, Found: MH^+: 335.1;

2-(1*H*-benzoimidazol-2-ylmethyl)-3-methyl-1*H*-benzoimidazole-5-carboxamidine (Compound 9), MS (ESI), Calculated for $C_{18}H_{18}N_6$: MH^+: 318.16, Found: MH^+: 319;

2-[1-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-1*H*-benzoimidazole-5-carboxylic acid (Compound 10), MS (ESI), Calculated for $C_{18}H_{16}N_6O_2$: MH^+: 348.4, Found: MH^+: 348.9;

2-[1-(1*H*-benzoimidazol-2-yl)-2-phenyl-ethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 11), MS (ESI), Calculated for $C_{23}H_{20}N_6$: MH^+: 380.17, Found: MH^+: 381;

2-[1-(1*H*-benzoimidazol-2-yl)-1-hydroxyethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 12), MS (BIOION), Calculated for $C_{17}H_{16}N_6O$: MH^+: 320.4, Found: MH^+: 321.2;

2-[1-(1*H*-benzoimidazol-2-yl)-1-methylethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 13), MS (ESI), Calculated for $C_{18}H_{18}N_6$: MH^+: 318.4, Found: MH^+: 319.1;

2-(1*H*-benzoimidazol-2-ylamino)-1*H*-benzoimidazole-5-carboxamidine (Compound 14), MS (ESI), Calculated for $C_{15}H_{13N8}$: MH^+: 291.1, Found: MH^+: 291.9;

1-methyl-2-[1-(1-methyl-1*H*-benzoimidazol-2-yl)ethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 15), MS (ESI), Calculated for $C_{19}H_{20}N_6$: MH^+: 332.2, Found: MH^+: 333;

2-[1-(5-benzoyl-1*H*-benzoimidazol-2-yl)ethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 16), MS (ESI), Calculated for $C_{24}H_{20}N_6O$: MH^+: 408.5, Found: MH^+: 409;

2-[1-(5,6-difluoro-1*H*-benzoimidazol-2-yl)-1-methylethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 17), MS (ESI), Calculated for $C_{18}H_{16}F_2N_6$: MH^+: 354.36, Found: MH^+: 355;

2-(1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridin-4-yl)-1*H*-benzoimidazole-5-carboxamidine (Compound 20), MS (ESI), Calculated for $C_{19}H_{18}N_6$: MH^+: 330.16, Found: MH^+: 331;

2-(5-chloro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 21), MS (BIOION), Calculated for $C_{16}H_{13}ClN_6$: MH^+: 324.7, Found: MH^-: 325;

2-(5-fluoro-1*H*-benzoimidazol-2-ylamino)-1*H*-benzoimidazole-5-carboxamidine

(Compound 22), MS (BIOION), Calculated for $C_{15}H_{12}F_{N8}$: MH^+: 309.3, Found: MH^+: 310.1;

2-(1*H*-naphtho[2,3-*d*]imidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 23), MS (BIOION), Calculated for $C_{20}H_{16}N_6$: MH^+: 340.4, Found: MH^+: 341.6;

2-[1-(4-hydroxy-1*H*-benzoimidazol-2-yl)-1-methylethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 24), MS (ESI), Calculated for $C_{18}H_{18}N_6O$: MH^+: 334.15, Found: MH^+: 335;

2-(5-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 25), MS (ESI), Calculated for $C_{16}H_{13}N_6F$: MH^+: 308.12, Found: MH^+: 349.9;

2-(5,6-dichloro-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridin-4-yl)-1*H*-benzoimidazole-5-carboxamidine (Compound 26), MS (BIOION), Calculated for $C_{19}H_{16}Cl_2N_6$: MH^+: 399.97, Found: MH^+: 401;

[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-6-hydroxy-3*H*-benzoimidazol-5-yl] phosphorate (Compound 27), MS (BIOION), Calculated for $C_{16}H_{15}N_6O_5P$: MH^+: 402.31, Found: MH^+: 403.4;

2-(5-bromo-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 28), MS (ESI), Calculated for $C_{16}H_{13}N_6Br$: MH^+: 368.06, Found: MH^+: 368.9;

2-(5,6-dichloro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 29), MS (ESI), Calculated for $C_{16}H_{12}Cl_2N_6$: MH^+: 358.05, Found: MH^+: 359;

2-(4,5,6-trifluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 30), MS (BIOION), Calculated for $C_{16}H_{11}N_6F_3$: MH^+: 344.1, Found: MH^+: 344.8;

2-(3*H*-imidazo[4,5-*c*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 31), MS (BIOION), Calculated for $C_{15}H_{13N8}$: MH^+: 291.31, Found: MH^+: 292;

2-[4-(3-phenylpropoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 32), MS (BIOION), Calculated for $C_{25}H_{24}N_6O$: MH^+: 424.2, Found: MH^+: 425.2;

2-(5-hydroxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 33), MS (ESI), Calculated for $C_{16}H_{14}N_6O$: MH^+: 306.3, Found: MH^+: 306.9;

2-{4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 34), MS (ESI), Calculated for $C_{21}H_{24}N_6O_3$: MH^+: 408.5,

Found: MH^+: 409.1;

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-yloxyacetic acid (Compound 35), MS (ESI), Calculated for $C_{28}H_{16}N_6O_3$: MH^+: 364.4, Found: MH^+: 364.9;

2-{5-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 36), MS (ESI), Calculated for $C_{21}H_{24}N_6O_3$: MH^+: 408.5, Found: MH^+: 409.1;

2-(1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 37), MS (BIOION), Calculated for $C_{15}H_{13N8}$: MH^+: 291.31, Found: MH^+: 292;

2-(7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 38), MS (BIOION), Calculated for $C_{16}H_{15N8}$: MH^+: 305.34, Found: MH^+: 306.1;

2-(6-bromo-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 39), MS (BIOION), Calculated for $C_{15}H_{12N8}Br$: MH^+: 370.21, Found: MH^+: 370.5;

2-(6-phenyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 40), MS (BIOION), Calculated for $C_{21}H_{17N8}$: MH^+: 367.41, Found: MH^+: 367.9;

2-(5-benzoyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 41), MS (BIOION), Calculated for $C_{23}H_{18}N_6O$: MH^+: 394.4, Found: MH^+: 395;

2-(5-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 42), MS (ESI), Calculated for $C_{17}H_{16}N_6$: MH^+: 304.14, Found: MH^+: 305;

2-(5,6-dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine Compound (43), MS (ESI), Calculated for $C_{18}H_{18}N_6$: MH^+: 318.16, Found: MH^+: 319;

2-[1-(1*H*-benzoimidazol-2-yl)-2-(1*H*-imidazol-2-yl)ethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 44), MS (ESI), Calculated for $C_{20}H_{18N9}$: MH^+: 370.16, Found: MH^+: 371.1;

2-[1-(1*H*-benzoimidazol-2-yl)-2-biphenyl-4-ylethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 45), MS (ESI), Calculated for $C_{29}H_{24}N_6$: MH^+: 456.2, Found: MH^+: 457.2;

2-(6-phenylethynyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 46), MS (BIOION), Calculated for $C_{23}H_{17}N_8$: MH^+: 391.43, Found: MH^+: 410.2;

2-(1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 47), MS (ESI), Calculated for $C_{17}H_{16}N_6$: MH^+: 304.1, Found: MH^+: 304.9;

2-(4,6-dichloro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 48), MS (BIOION), Calculated for $C_{16}H_{13}ClN_6$: MH^+: 359.2, Found: MH^+: 359.3;

2-(1*H*-phenanthro[9,10-*d*]imidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 49), MS (BIOION), Calculated for $C_{24}H_{18}N_6$: MH^+: 390.45, Found: MH^+: 390.7;

2-(1-methyl-6-trifluoromethyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 50), MS (BIOION), Calculated for $C_{17}H_{14}N_8F_3$: MH^+: 373.34, Found: MH^+: 374.6;

2-[1-(1*H*-benzoimidazol-2-yl)-2-naphthalen-1-ylethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 51), MS (ESI), Calculated for $C_{27}H_{22}N_6$: MH^+: 430.19, Found: MH^+: 431.1;

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-*N*-butyl-3*H*-benzoimidazole-4-carboxamide (Compound 52), MS (BIOION), Calculated for $C_{21}H_{23}N_8O$: MH^+: 389.2, Found: MH^+: 390.4;

2-(7-chloro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 53), MS (ESI), Calculated for $C_{17}H_{15}N_6Cl$: MH^+: 338.1, Found: MH^+: 338.9;

2-(5-chloro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 54), MS (ESI), Calculated for $C_{17}H_{15}N_6Cl$: MH^+: 338.1, Found: MH^+: 338.9;

4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amindino-1*H*-benzoimidazol-2-yl)ethyl]benzoic

acid (Compound 55), MS (ESI), Calculated for $C_{24}H_{20}N_6O_2$: MH^-: 424.16, Found: MH^-:;

2-(7,8-dimethyl-1,2,3,4-tetrahydrobenzo[4,5]imidazo[1,2-*a*]pyridin-4-yl)-1*H*-benzoimidazole-5-carboxamidine (Compound 56), MS (ESI), Calculated for $C_{21}H_{22}N_6$: MH^+: 358.19, Found: MH^+: 359;

2-(4,6-dichloro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 57), MS (ESI), Calculated for $C_{17}H_{14}N_6Cl_2$: MH^+: 372.07, Found: MH^+: 373;

2-(6-bromo-4,5-dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 58), MS (ESI), Calculated for $C_{18}H_{17}N_6Br$: MH^+: 396.09, Found: MH^+: 396.4; and

2-(4,5-dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 59), MS (BIOION), Calculated for $C_{18}H_{18}N_6$: MH^+: 318.16, Found: MH^+: 319.

EXAMPLE 11

2-(6-Fluoro-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 60),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl, C comprises 6-fluoro-4-imidazol-1-yl-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture comprising ethyl (5-amidino-1*H*-benzoimidazol-2-yl)acetate hydrochloride (1.34 g, 4.73 mmol), 6-amino-4-fluoro-2-(1*H*-imidazol-1-yl)aniline (1.0 g, 4.73 mmol) and DMPU (3 mL) was heated in a sealed tube for 2 hours at 175 °C. The mixture was cooled to 60 °C, diluted with methanol (3 mL) and then added dropwise to vigorously stirring acetonitrile (300 mL) to give a precipitate. The precipitate was collected and dried under vacuum. The residue was dissolved in 1N hydrochloric acid and purified by reverse-phase C-18 HPLC (2-27% gradient) to give 2-(6-fluoro-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (600 mg, 1.12 mmol), MS (BIOION), Calculated for $C_{19}H_{15}FN_9$: MH^+: 374.37; Found: MH^+: 375.8.

Proceeding as in Example 11, but substituting other starting materials, provided the following compounds of Formula I:

2-benzothiazol-2-ylmethyl-1*H*-benzoimidazole-5-carboxamidine (Compound 61), MS (BIOION), Calculated for $C_{16}H_{13}N_5S$: MH^+: 307.3, Found: MH^+: 308.3;

2-(5-trifluoromethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 62), MS (BIOION), Calculated for $C_{17}H_{13}N_6F_3$: MH^-: 358.12, Found: MH^+: 359;

2-(4-hydroxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 63), MS (ESI), Calculated for $C_{16}H_{14}N_6O$: MH^+: 306.12, Found: MH^-: 306.5;

2-(4-hydroxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 64), MS (BIOION), Calculated for $C_{17}H_{16}N_6O$: MH^+: 320.14, Found: MH^+: 321.4;

2-(5,6-dimethoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 65), MS (BIOION), Calculated for $C_{18}H_{18}N_6O_2$: MH^-: 350.38, Found: MH^+: 351.1;

2-(1*H*-imidazo[4,5-*f*]quinolin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 66), MS (BIOION), Calculated for $C_{19}H_{15}N_8$: MH^+: 341.14, Found: MH^-: 342;

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-4-carboxylic acid (Compound 67), MS (BIOION), Calculated for $C_{17}H_{14}N_6O_2$: MH^+: 334.12, Found: MH^+: 335;

2-[5-(2,3-dihydroxypropoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 68), MS (ESI), Calculated for $C_{19}H_{20}N_6O_3$: MH^+: 380.4, Found: MH^+: 381;

2-(5-sulfamoyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 69), MS (ESI), Calculated for $C_{17}H_{17}N_8O_2S$: MH^+: 383.12, Found: MH^+: 384;

2-(1-methyl-5-sulfamoyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 70), MS (ESI), Calculated for $C_{16}H_{15}N_8O_2S$: MH^+: 369.1, Found: MH^+: 369.8;

2-(5-benzylsulfamoyl-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 71), MS (ESI), Calculated for $C_{24}H_{23}N_8O_2S$: MH^+: 473.1, Found: MH^+: 474.1;

2-(5-ethoxy-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 72), MS (BIOION), Calculated for $C_{17}H_{17}N_8O$: MH^+: 335.37, Found: MH^+: 354.1;

2-(5-methoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 73), MS (BIOION), Calculated for $C_{17}H_{16}N_6O$: MH^+: 320.35, Found: MH^+: 320.8;

2-(4,6-dibromo-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 74), MS (BIOION), Calculated for $C_{16}H_{12}Br_2N_6$: MH^+: 448.1, Found: MH^+: 448.9;

2-(1*H*-imidazo[4,5-*g*]quinoxalin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 75), MS (BIOION), Calculated for $C_{18}H_{14}N_9$: MH^+: 342.4, Found: MH^+: 343.5;

2-(1-furan-2-ylmethyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 76), MS (BIOION), Calculated for $C_{20}H_{17}N_8O$: MH^+: 371.4, Found: MH^+: 372.3;

2-(3-cyclopropyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 77), MS (BIOION), Calculated for $C_{18}H_{17}N_8$: MH^+: 331.38, Found: MH^+: 332.4;

2-[1-(1*H*-benzoimidazol-2-yl)-2-(4-bromophenyl)ethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 78), MS (ESI), Calculated for $C_{23}H_{19}N_6$: MH^+: 379.17, Found: MH^+: 379.9;

(*S*)-2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(pyrrolidin-3-yloxy)phenyl]ethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 79), MS (ESI), Calculated for $C_{27}H_{27}N_8O$: MH^+: 465.23, Found: MH^+: 466.2;

2-(6-chloro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 80), MS (BIOION), Calculated for $C_{17}H_{15}ClN_6$: MH^+: 338.7, Found: MH^+: 339.2;

2-(4,6-dichloro-1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-

5-carboxamidine (Compound 81), MS (BIOION), Calculated for $C_{17}H_{14}Cl_2N_6$: MH^+: 373.2, Found: MH^+: 374;

2-(1-(1*H*-benzoimidazol-2-yl)-2-{4-[1-(1-iminoethyl)pyrrolidin-3-yloxy]phenyl}ethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 82), MS (ESI), Calculated for $C_{29}H_{30}N_9O$: MH^+: 506.25, Found: MH^+: 507.3;

2-(4,6-bismethylsulfanyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 83), MS (ESI), Calculated for $C_{18}H_{18}N_6S_2$: MH^+: 382.1, Found: MH^+: 382.9;

2-(4,6-dimethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 84), MS (ESI), Calculated for $C_{18}H_{18}N_6$: MH^+: 318.4, Found: MH^+: 318.8;

2-(4-nitro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 85), MS (ESI), Calculated for $C_{16}H_{13}N_8O_2$: MH^+: 335.1, Found: MH^+: 335.9;

2-(7-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-*N*-hydroxy-1*H*-benzoimidazole-5-carboxamidine (Compound 86), MS (BIOION), Calculated for $C_{16}H_{15}N_8O$: MH^+: 321.34, Found: MH^+: 322;

2-(3,7-dimethyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 87), MS (BIOION), Calculated for $C_{17}H_{17}N_8$: MH^+: 319.37, Found: MH^+: 319.9;

2-[3-(2-hydroxyethyl)-7-methyl-3*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 88), MS (BIOION), Calculated for $C_{18}H_{19}N_8O$: MH^+: 349.39, Found: MH^+: 350.1;

2-(1,3-dimethyl-2,6-dioxo-2,3,6,7-tetrahydro-1*H*-purin-8-ylmethyl)-1*H*-benzoimidazole-

5-carboxamidine (Compound 89), MS (BIOION), Calculated for $C_{16}H_{16}N_9O_2$: MH^+: 352.35, Found: MH^+: 352.5;

2-(4,6-difluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 90), MS (BIOION), Calculated for $C_{16}H_{12}F_2N_6$: MH^+: 326.3, Found: MH^+: 327;

2-(2,6-dithioxo-2,3,6,9-tetrahydro-1*H*-purin-8-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 91), MS (BIOION), Calculated for $C_{14}H_{12}N_9S_2$: MH^+: 356.4, Found: MH^+: 357.4;

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-sulfonic acid (Compound 92), MS (ESI), Calculated for $C_{16}H_{14}N_6SO_3$: MH^+: 370.4, Found: MH^+: 370.9;

2-[5-(1*H*-tetrazol-5-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 93), MS (ESI, Calculated for $C_{17}H_{14}N_{10}$: MH^+: 358.4, Found: MH^+: 358.9;

2-(7*H*-purin-8-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 94), MS (ESI), Calculated for $C_{14}H_{12}N_9$: MH^+: 292.3, Found: MH^+: 292.9;

2-[1-methyl-5-(morpholin-4-ylsulfonyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 95), MS (ESI), Calculated for $C_{21}H_{23}N_8SO_3$: MH^+: 453.1, Found: MH^+: 454.1;

2-(5-benzylsulfamoyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 96), MS (ESI), Calculated for $C_{23}H_{21}N_8SO_2$: MH^+: 459.15, Found: MH^+: 460;

2-{5-[2-(2-hydroxyethoxy)ethylsulfamoyl]-1-methyl-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 97), MS (ESI), Calculated for $C_{21}H_{25}N_8SO_4$: MH^+: 471.2, Found: MH^+: 472.1;

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-4-yloxyacetic acid (Compound 98), MS (ESI), Calculated for $C_{18}H_{16}N_6O_3$: MH^+: 364.4, Found: MH^+: 365;

2-[5-(1,3-dioxo-1,3-dihydroisoindol-2-ylmethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 99), MS (ESI), Calculated for $C_{25}H_{19}N_8O_2$: MH^+: 449.5, Found: MH^+: 450.1;

2-[4-(2-methoxyethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 100), MS (ESI), Calculated for $C_{18}H_{18}N_6O_2$: MH^+: 350.4, Found: MH^+: 351;

2-{4-[2-(2-hydroxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 101), MS (ESI), Calculated for $C_{20}H_{22}N_6O_3$: MH^+: 394.4, Found: MH^+: 395.1;

2-[5-(2,3-dihydroxypropylsulfamoyl)-1-methyl-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 102), MS (ESI), Calculated for $C_{20}H_{23}N_8SO_4$: MH^+: 457.15, Found: MH^+: 458.1;

2-{5-[bis-(2-methoxyethyl)sulfamoyl]-1-methyl-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 103), MS (ESI), Calculated for $C_{23}H_{29}N_8SO_4$: MH^+: 499.1, Found: MH^+: 500.2;

2-(4,5,6,7-tetrachloro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 104), MS (BIOION), Calculated for $C_{16}H_{10}Cl_4N_6$: MH^+: 428.1, Found: MH^+: 429;

2-(5-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 105), MS (ESI), Calculated for $C_{19}H_{16}N_9$: MH^+: 356.4, Found: MH^+: 356.5;

2-[4-(4-chlorophenoxymethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 106), MS (ESI), Calculated for $C_{24}H_{21}N_6ClO_2$: MH^+: 460.9, Found: MH^+: 461.1;

2-[4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 107), MS (ESI), Calculated for $C_{22}H_{22}N_6O_2$: MH^+: 390.4, Found: MH^+: 391;

2-[1-methyl-5-(2-morpholin-4-ylethylsulfamoyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 108), MS (ESI), Calculated for $C_{23}H_{28}N_9SO_3$: MH^+: 496.2, Found: MH^+: 496.4;

2-(6,7,8,9-tetrahydrodipyrido[1,2-*a*;2',3'-*d*]imidazol-9-yl)-1*H*-benzoimidazole-5-carboxamidine (Compound 109), MS (ESI), Calculated for $C_{18}H_{17}N_8$: MH^+: 331.38, Found: MH^+: 331.9;

2-(4-{2-[2-(2-hydroxyethoxy)ethoxy]ethoxy}-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 110), MS (ESI), Calculated for $C_{22}H_{26}N_6O_4$: MH^+: 438.5, Found: MH^+: 438.5;

2-[4-(2-methoxyethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 111), MS (ESI), Calculated for $C_{19}H_{20}N_6O_2$: MH^+: 364.4, Found: MH^+: 364.5;

2-(4,6-dimethoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 112), MS (BIOION), Calculated for $C_{18}H_{18}N_6O_2$: MH^+: 350.15, Found: MH^+: 351.1;

2-(5,7-dimethyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 113), MS (BIOION), Calculated for $C_{17}H_{17}N_8$: MH^-: 319.37, Found: MH^+: 320.2;

2-(4,6-bis(methylsulfonyl)-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 114), MS (BIOION), Calculated for $C_{18}H_{18}N_9S_2O_4$: MH^-: 446.08, Found: MH^-: 447.3;

2-(4-heptyloxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 115), MS (ESI), Calculated for $C_{23}H_{28}N_6O$: MH^+: 404.5, Found: MH^+: 405.1;

N-hydroxy-2-{4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 116), MS (ESI), Calculated for $C_{21}H_{24}N_6O_4$: MH^-: 424.5, Found: MH^+: 425.2;

2-(1*H*-benzoimidazol-2-ylmethyl)-6-chloro-1*H*-benzoimidazole-5-carboxamidine (Compound 117), MS (ESI), Calculated for $C_{16}H_{13}ClN_6$: MH^+: 324.09, Found: MH^-: 324.4;

2-[5-(pyridin-3-ylmethylsulfamoyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 118), MS (ESI), Calculated for $C_{22}H_{20}N_9SO_2$: MH^+: 460.14, Found: MH^+: 460.5;

2-(1*H*-benzoimidazol-2-ylmethyl)-6-fluoro-1*H*-benzoimidazole-5-carboxamidine (Compound 119), MS (ESI), Calculated for $C_{16}H_{13}N_6F$: MH^+: 308.12, Found: MH^+: 308.4;

2-(5-methyl-1*H*-imidazo[4,5-*b*]pyridin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 120), MS (BIOION), Calculated for $C_{16}H_{15}N_8$: MH^+: 305.34, Found: MH^+: 306.5;

2-[5-(2-morpholin-4-ylethylsulfamoyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 121), MS (ESI), Calculated for $C_{21}H_{26}N_9SO_3$: MH^+: 482.18, Found: MH^+: 482.4;

2-[4,6-di(2-methoxyethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 122), MS (BIOION), Calculated for $C_{22}H_{26}N_6O_4$: MH^-: 438.2, Found: MH^+: 439.2;

2-(4-cyclopropylmethoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 123), MS (ESI), Calculated for $C_{20}H_{20}N_6O$: MH^+: 360.4, Found: MH^+: 361;

2-(6-fluoro-4-methoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 124), MS (ESI), Calculated for $C_{17}H_{15}FN_6O$: MH^+: 338.13; Found: MH^+: 338.9;

2-[6-fluoro-4-(2-methoxyethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 125), MS (ESI), Calculated for $C_{19}H_{19}FN_6O_2$: MH^+: 382.16; Found: MH^+: 383;

2-(1*H*-benzoimidazol-2-ylmethyl)-7-chloro-1*H*-benzoimidazole-5-carboxamidine (Compound 126), MS (ESI), Calculated for $C_{16}H_{13}ClN_6$: MH^+: 324.09; Found: MH^+: 324.8;

2-(1*H*-benzoimidazol-2-ylmethyl)-7-chloro-1*H*-benzoimidazole-5-carboxamidine (Compound 127), MS (ESI), Calculated for $C_{16}H_{17}N_9$: MH^+: 335.16; Found: MH^+: 335.9;

2-(1*H*-benzoimidazol-2-ylmethyl)-*N*-methoxy-1*H*-benzoimidazole-5-carboxamidine (Compound 128), MS (ESI), Calculated for $C_{17}H_{16}N_6O$: MH^+: 320.4; Found: MH^+: 320.9;

N-methoxy-2-{4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 129), MS (ESI), Calculated for $C_{22}H_{26}N_6O_4$: MH^+: 438.5; Found: MH^+: 439.2;

2-(8-hydroxyquinolin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 130), ^1H NMR d 9.4 (bs, 1.5 H), 9.0 (bs, 1.5 H), 8.49 (m, 1 H), 8.20 (bs, 1 H), 7.7 (m, 3 H), 7.5 (s, 2 H), 7.2 (bs, 1 H), 4.8 (bs, 2 H). LRMS (EI) calcd $C_{12}H_{11}NO_3$ + H 318.1; found 317.9;

2-{4-[2-(2-hydroxyethoxy)ethylsulfamoyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 131), MS (ESI), Calculated for $C_{20}H_{23}N_8SO_2$: MH^+: 457.15; Found: MH^+: 458;

2-{1-[2-(2-methoxyethoxy)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 132), MS (ESI), Calculated for $C_{21}H_{24}N_6O_2$: MH^+: 392.5; Found: MH^+: 393;

2-{1-[2-(2-hydroxyethoxy)ethyl]-4-methyl-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 133), MS (BIOION), Calculated for $C_{20}H_{23}N_8O_2$: MH^+: 393.45; Found: MH^+: 394.1;

2-{6-fluoro-4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 134), MS (BIOION), Calculated for $C_{21}H_{23}FN_6O_3$: MH^+: 426.18; Found: MH^+: 427.2;

2-(6-chloro-4-dimethylsulfamoyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 135), MS (ESI), Calculated for $C_{16}H_{14}Cl_8SO_2$: MH^+: 403.06; Found: MH^+: 404;

2-(6-methylsulfonyl-4-methoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 136), MS (BIOION), Calculated for $C_{18}H_{18}N_6SO_3$: MH^+: 398.12; Found: MH^+: 399.3;

2-(6-fluoro-4-methylsulfonyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 137), MS (BIOION), Calculated for $C_{17}H_{15}FN_6SO_2$: MH^+: 386.1; Found: MH^+: 387;

2-[5-(2-amino-2,3-dihydroimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 138), MS (ESI), Calculated for $C_{19}H_{17}N_8$: MH^+: 371.4; Found: MH^+: 372;

2-(5-cyclopropylmethoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 139), MS (ESI), Calculated for $C_{20}H_{20}N_6O$: MH^+: 360.4; Found: MH^+: 361.1;

2-[6-fluoro-4-(4-methoxyphenoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 140), MS (BIOION), Calculated for $C_{23}H_{19}FN_6O_2$: MH^+: 430.44; Found: MH^+: 431;

2-{6-chloro-4-[2-(2-hydroxyethoxy)ethylsulfamoyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 141), MS (ESI), Calculated for $C_{20}H_{22}ClN_8SO_4$: MH^+: 491.11; Found: MH^+: 492.1;

2-(6-fluoro-4-morpholin-4-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 142), MS (BIOION), Calculated for $C_{20}H_{20}F_{N8}O$: MH^+: 393.42; Found: MH^+: 394;

2-{6-fluoro-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 143); ^1H NMR (300 MHz, D_6-DMSO): δ 1.8-1.95

(m, 2H), 2.19 (t, 2H, J = 8.0), 3.50 (t, 2H, J = 6.9), 3.61 (t, 2H, J = 5.2), 4.35 (t, 2H, J = 5.2), 5.20 (s,2H), 7.15 (dd, 1H, J = 11.8, 1.7), 7.24 (dd, 1H, J = 8.2, 1.7), 7.84 (d, 1H, J = 8.5), 7.90 (d, 1H, J = 8.5), 8.27 (s, 1H), 9.35 (bs, 2H), 9.65 (bs, 2H); MS (BIOION), Calculated for $C_{22}H_{22}FN_8O_2$: MH^+: 435.18; Found: MH^+: 436.4;

2-[4-(2,3-dihydrobenzo[1,4]dioxin-2-ylmethoxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 144), MS (BIOION), Calculated for $C_{25}H_{21}FN_6O_3$: MH^+: 472.2; Found: MH^+: 473.3;

2-[6-fluoro-4-(2-methoxybenzyloxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 145), MS (BIOION), Calculated for $C_{24}H_{21}FN_6O_2$: MH^+: 444.2; Found: MH^+: 445.4;

2-benzothiazol-2-ylmethyl-*N*-hydroxy-1*H*-benzoimidazole-5-carboxamidine (Compound 146), MS (BIOION), Calculated for $C_{16}H_{13}N_5SO$: MH^+: 323.37; Found: MH^+: 325.1;

2-[6-fluoro-4-(3-morpholin-4-ylphenoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 147), MS (BIOION), Calculated for $C_{26}H_{24}FN_8O_2$: MH^+: 458.52; Found: MH^+: 485.6;

2-[4-(benzo[1,3]dioxol-5-yloxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 148), MS (ESI), Calculated for $C_{23}H_{17}FN_6O_3$: MH^+: 444.13; Found: MH^+: 445;

2-[4-(2,6-dimethoxyphenoxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 149), MS (BIOION), Calculated for $C_{24}H_{21}FN_6O_3$: MH^+: 460.47; Found: MH^+: 459;

2-{4-[2-(2,5-dioxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 150); ^1H NMR (300 MHz, D_6-DMSO): δ 2.65 (s, 4H), 3.77 (t, 2H, J = 5.7), 4.42 (t, 2H, J = 5.7), 5.20 (s, 2H), 7.15 (d, 1H, J = 11.8), 7.24 (d, 1H, J = 8.1), 7.82 (d, 1H, J = 8.7), 7.88 (d, 1H, J = 8.5), 8.27 (s, 1H), 9.35 (bs, 2H), 9.60 (bs, 2H); MS (BIOION), Calculated for $C_{22}H_{20}FN_8O_3$: MH^+: 449.16; Found: MH^+: 450;

2-[6-fluoro-4-(4-imidazol-1-ylphenoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 151), MS (BIOION), Calculated for $C_{25}H_{19}FN_9O$: MH^+: 466.48; Found: MH^+: 467.4;

2-[6-fluoro-4-(4-piperazin-1-ylphenoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 152), MS (ESI), Calculated for $C_{26}H_{25}FN_9O$: MH^+: 484.21; Found: MH^+: 485;

2-(1*H*-benzoimidazol-2-ylmethyl)-7-methyl-1*H*-benzoimidazole-5-carboxamidine (Compound 153), MS (ESI), Calculated for $C_{17}H_{16}N_6$: MH^+: 304.4; Found: MH^+: 305;

2-{6-fluoro-4-[2-(2-oxoimidazolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 154), MS (BIOION), Calculated for $C_{21}H_{21}FN_9O_2$: MH^+: 436.45; Found: MH^-: 437.8;

2-(4-benzo[1,3]dioxol-5-ylmethoxy-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 155), MS (ESI), Calculated for $C_{24}H_{19}FN_6O_3$: MH^+: 458.15; Found: MH^-: 459.1;

(*S*)-2-[6-fluoro-4-(5-oxopyrrolidin-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 156), MS (ESI), Calculated for $C_{21}H_{20}F_{N8}O_2$: MH^+: 421.17; Found: MH^+: 422.1;

2-(4,6-diimidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 157), MS (BIOION), Calculated for $C_{22}H_{18}N_{10}$: MH^+: 422.45; Found: MH^+: 423.5;

2-(1*H*-benzoimidazol-2-ylmethyl)-*N*-hydroxy-1*H*-imidazo[4,5-*b*]pyridine-5-carboxamidine (Compound 158), MS (BIOION), Calculated for $C_{15}H_{13}N_8$: MH^+: 291.12; Found: MH^+: 292.5;

2-(4,6-difluoro-5-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 159), MS (BIOION), Calculated for $C_{19}H_{14}F_2N_9$: MH^+: 392.37; Found: MH^+: 393.4;

2-[6-fluoro-4-(2,2,2-trifluoroethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 160), MS (BIOION), Calculated for $C_{18}H_{14}F_4N_6O$ MH^+: 406.12; Found: MH^+: 407.2;

2-{6-fluoro-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-*N*-hydroxy-1*H*-benzoimidazole-5-carboxamidine (Compound 161), MS (BIOION), Calculated for $C_{22}H_{22}FN_8O_3$: MH^+: 451.18; Found: MH^+: 452.2;

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 162), MS (ESI), Calculated for

$C_{22}H_{23}F_2N_8O_2$: MH^+: 439.19;

Found: MH^+: 440.1;

2-{4-[(benzo[1,3]dioxol-5-ylmethyl)sulfamoyl]-6-chloro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 163), MS (ESI), Calculated for $C_{24}H_{20}ClN_8SO_2$: MH^+: 537.1; Found: MH^+: 538.2;

2-(4,6-difluoro-1*H*-benzoimidazol-2-ylmethyl)-*N*-hydroxy-1*H*-benzoimidazole-5-carboxamidine (Compound 164), MS (BIOION), Calculated for $C_{16}H_{12}F_2N_6O$: MH^+: 342.31; Found: MH^+: 343.2;

2-[4-(1-azabicyclo[2.2.2]oct-3-yloxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 165), MS (BIOION), Calculated for $C_{23}H_{24}FN_8O$: MH^+: 433.49; Found: MH^+: 434.6;

2-(5-[1,2,4]triazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 166), MS (ESI), Calculated for $C_{18}H_{15}N_9$: MH^+: 357.38; Found: MH^+: 358;

2-[5-(4-imidazol-1-ylphenoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 167), MS (ESI), Calculated for $C_{25}H_{20}N_9O$: MH^+: 448.49; Found: MH^+: 449.1;

2-(5-[1,2,3]triazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 168), MS (ESI), Calculated for $C_{18}H_{15}N_9$: MH^+: 357.38; Found: MH^+: 358;

2-(5-pyrazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 169), MS (ESI), Calculated for $C_{19}H_{16}N_9$: MH^+: 356.39; Found: MH^+: 357;

2-(4-amino-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 170), MS (ESI), Calculated for $C_{16}H_{14}FN_8$: MH^+: 323.33; Found: MH^+: 323.9;

2-{4-[4-(4-acetylpiperazin-1-yl)phenoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 171), MS (ESI), Calculated for $C_{28}H_{27}FN_9O_2$: MH^+: 526.22; Found: MH^+: 527.2;

2-(5-cyano-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine

(Compound 172), MS (BIOION), Calculated for $C_{17}H_{13}N_8$: MH^+: 315.12; Found: MH^+: 315.9;

2-(6-fluoro-4-pyrrolidin-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 173), MS (BIOION), Calculated for $C_{20}H_{20}FN_8$: MH^+: 377.42; Found: MH^+: 377.6;

2-[4-(4-benzylpiperazin-1-ylsulfonyl)-6-chloro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 175), MS (ESI), Calculated for $C_{27}H_{27}ClN_9SO_2$: MH^+: 562.17; Found: MH^+: 563.3;

2-(6-fluoro-4-isobutoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 176), MS (ESI), Calculated for $C_{20}H_{21}FN_6O$: MH^+: 380.18; Found: MH^+: 381.1;

2-[5-(2-methylimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 177), MS (BIOION), Calculated for $C_{20}H_{18}N_9$: MH^+: 370.2; Found: MH^+: 371.4;

2-[4-(2,2-dimethylpropoxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 178), MS (ESI), Calculated for $C_{21}H_{23}FN_6O$: MH^+: 394.19; Found: MH^+: 395.1;

2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamide (Compound 179), MS (BIOION), Calculated for $C_{17}H_{15}N_8O$: MH^+: 333.13; Found: MH^+: 334.2;

N-hydroxy-1-methyl-2-(1-methyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 180), MS (BIOION), Calculated for $C_{18}H_{18}N_6O$: MH^+: 334.15; Found: MH^+: 335.1;

2-(1*H*-benzoimidazol-2-ylmethyl)-1-(3-imidazol-1-ylpropyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 181), MS (BIOION), Calculated for $C_{22}H_{21}N_9$: MH^+: 398.47; Found: MH^+: 399.3;

2-[5-(2-methyl-2*H*-tetrazol-5-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 182), MS (BIOION), Calculated for $C_{18}H_{16}N_{10}$: MH^+: 372.16; Found: MH^+: 373.2;

2-[4-(benzo[1,3]dioxol-5-ylmethoxy)-6-imidazol-1-yl-

1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 183), MS (BIOION), Calculated for $C_{27}H_{22}N_9O_3$: MH^+: 506.2; Found: MH^+: 507;

2-(5-fluoro-6-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 184), MS (BIOION), Calculated for $C_{19}H_{15}FN_9$: MH^+: 374.38; Found: MH^+: 375.3;

2-(6-fluoro-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 185); ^{1}H NMR (300 MHz, D_6-DMSO): δ 2.37 (d, 3H, *J* = 1.2), 4.83 (s, 2H), 7.60 (dd, 1H, *J* = 8.7, 2.2), 7.70 (dd, 1H, *J* = 10.4, 1.7), 7.76 (dd, 1H, *J* = 8.7, 1.7), 7.84 (d, 1H, *J* = 8.7), 8.21 (d, 1H, *J* = 1.2), 8.29 (t, 1H, *J* = 1.7), 9.19 (bs, 2H), 9.47 (bs, 2H), 9.97 (t, 1H, *J* = 1.7); MS (BIOION), Calculated for $C_{20}H_{17}FN_9$: MH^+: 388.41, Found: MH^+: 387.8;

2-[7'-(benzo[1,3]dioxol-5-ylmethoxy)-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 186), MS (BIOION), Calculated for $C_{31}H_{24}N_9O_3$: MH^+: 556.2; Found: MH^+: 557.8;

2-{7'-[2-(2-oxopyrrolidin-1-yl)ethoxy]-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 187), MS (BIOION), Calculated for $C_{29}H_{27}N_9O_2$: MH^+: 533.2; Found: MH^+: 534.2;

2-{7'-[2-(2-oxopyrrolidin-1-yl)ethoxy]-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 188), MS (BIOION), Calculated for $C_{25}H_{25}N_9O_2$: MH^+: 483.2; Found: MH^+: 484.6;

2-[6-fluoro-4-(2-isopropylimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 189); ^{1}H NMR (300 MHz, D_6-DMSO): δ 1.14 (d, 6H, J = 6.9), 3.01 (m, 1H), 4.97 (s, 2H), 7.58 (dd, 1H, J = 9.9, 2.2), 7.78 (dd, 1H, J = 8.7, 2.5), 7.83 (d, 1H, J = 2.0), 7.89 (d, 1H, J = 2.0), 7.90 (dd, 1H, J = 8.2, 1.2), 7.96 (d, 1H, J = 8.7), 8.31 (s, 1H), 9.37 (bs, 2H), 9.65 (bs, 2H); MS (BIOION), Calculated for $C_{22}H_{21}FN_9$: MH^+: 416.46; Found: MH^+: 417.6;

2-{4-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 190), MS (ESI), Calculated for $C_{26}H_{20}FN_8O_3$: MH^+: 497.16; Found: MH^+: 498.2;

N-{2-[2-(5-amidino-

1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}acetamide (Compound 191), MS (BIOION), Calculated for $C_{20}H_{21}N_8O$: MH^+: 375.18; Found: MH^+: 376.2;

2-[6-fluoro-4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 192); ^{1}H NMR (300 MHz, D_6-DMSO): δ 1.70-2.05 (m, 4H), 3.67 (m, 1H), 3.78 (m, 1H), 4.16-4.25 (m, 3H), 4.94 (s, 2H), 7.09 (dd, 1H, *J* = 12.1, 2.0), 7.20 (dd, 1H, *J* = 8.4, 2.0), 7.72 (dd, 1H, *J* = 8.7, 1.7), 7.80 (d, 1H, *J* = 8.4), 8.17 (d,

1H, *J* = 1.0), 9.18 (bs, 2H), 9.43 (bs, 2H); ^{13}C NMR (75 MHz, D_6-DMSO): δ 25.27, 26.54, 27.48, 67.60, 71.55, 76.20, 96.99 (dd, *J* = 316.5, 30.5), 114.82, 115.97, 119.28, 122.60, 123.27, 132.84 (d, *J* = 16.6), 135.87, 138.99, 147.14 (d, *J* = 13.5), 148.31, 150.97, 158.93, 162.46, 165.79; Plasma TOF MS 409.2 ($M+H^+$);

2-[6-fluoro-4-(2-methylimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 193); ^{1}H NMR (300 MHz, D_6-DMSO): δ 2.53 (s, 3H), 5.00 (s, 2H), 7.50 (dd, 1H, *J* = 9.9, 2.2), 7.75 (dd, 1H, *J* = 8.7, 2.2), 7.80 (d, 1H, *J* = 2.0), 7.91 (dd, 1H, *J* = 8.9, 1.5), 7.95 (s, 1H), 7.98 (d, 1H, *J* = 2.0), 8.33 (s, 1H), 9.42 (bs, 2H), 9.69 (bs, 2H); ^{13}C NMR (75 MHz, D_6-DMSO): δ 10.77, 27.51, 105.52 (dd, *J* = 457.1, 27.0), 114.65, 115.36, 118.47, 122.53 (d, *J* = 13.5), 123.85, 124.40, 124.80, 132.33 (d, *J* = 17.7), 135.62, 137.16, 137.38, 145.44, 150.81, 151.97, 155.95, 159.53, 165.43; Plasma TOF MS 389.8 ($M+H^+$);

2-{4-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 194); ^{1}H NMR (300 MHz, D_6-DMSO): δ 2.05-2.18 (m, 2H), 2.32-2.35 (m, 2H), 3.05-3.15 (m, 2H), 3.75 (t, 2H, *J* = 5.7), 4.35 (t, 2H, *J* = 5.7), 4.82 (s, 2H), 5.73 (t, 2H, *J* = 1.8), 7.0 (dd, 1H, *J* = 11.6, 1.4), 7.15 (dd, 1H, *J* = 8.4, 1.8), 7.68 (dd, 1H, *J* = 8.6, 1.5), 7.77 (d, 1H, *J* = 8.5), 8.12 (s, 1H), 9.05 (bs, 2H), 9.35 (bs, 2H);

2-[1-(4-butyl-1*H*-benzoimidazol-2-yl)-1-methylethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 195);

2-(1-butyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 196);

2-(1-phenyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine

(Compound 197);

2-(7-butyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 198);

2-[3-(3-phenylpropyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 199);

2-[1-(4-hydroxyphenyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 201);

2-(5-*tert*-butyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 202);

2-(5-bromo-1-cyclohexa-1,3,4-trienyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 203);

2-{1-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 204);

2-[1-(2-hydroxyethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 205);

2-(6-fluoro-4-phenoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 206);

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 207);

2-[4-(2-dimethylaminoethoxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 208);

2-[6-fluoro-4-(2-imidazol-1-ylethylamino)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 209);

2-[6-fluoro-4-(2-pyridin-2-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 210);

2-(6-ethoxy-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 211);

2-(6-fluoro-4-tetrahydropyran-2-ylmethoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 212);

2-{6-fluoro-4-[2-(4-methylthiazol-5-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-

1*H*-benzoimidazole-5-carboxamidine (Compound 213);

2-{6-fluoro-4-[2-(2-oxooxazolidin-3-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 214);

2-{4-[2-(3,3-dimethyl-2-oxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 215);

2-{4-[2-(1,3-dioxooctahydroisoindol-2-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-

1*H*-benzoimidazole-5-carboxamidine (Compound 216);

3-benzylsulfonyl-*N*-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]propionamide (Compound 217);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]pyridine-2-carboxamide (Compound 218).

2-{6-fluoro-4-[2-(1-methylpyrrolidin-2-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 219);

2-{1-[2-(1-iminoethylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 220);

2-(5-nitro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 221);

2-[4-(2-morpholin-4-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 222);

2-[6-fluoro-1-methyl-4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 225);

2-{6-fluoro-4-[2-(2-methoxyethoxy)ethoxy]-1-methyl-1*H*-benzoimidazol-2-ylmethyl}-3*H*-benzoimidazole-5-carboxamidine (Compound 226);

2-pridin-2-ylmethyl-3*H*-benzoimidazole-5-carboxamidine (Compound 230);

2-(1'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 309), MS (BIOION), Calculated for $C_{25}H_{18}N_9$: MH^+: 406.45; Found: MH^+: 407;

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-*N*-hydroxy-1*H*-benzoimidazole-5-carboxamidine (Compound 310);

2-(1*H*-benzoimidazol-2-ylmethyl)-*N*-hydroxy-6-methoxy-1*H*-benzoimidazole-

5-carboxamidine (Compound 311);

2-(7'-ethoxy-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 312);

ethyl *C*-(2-(1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-yl)iminomethylcarbamate (Compound 313);

2-[6-chloro-4-(2-piperidin-1-ylethylsulfamoyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 314);

N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}benzamide (Compound 315);

2-[5-(*N*-hydroxyamidino)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxylic acid (Compound 317);

2-benzo[4,5]imidazo[1,2-*a*]pyridin-4-yl-1*H*-benzoimidazole-5-carboxamidine (Compound 318);

2-(6-methylquinolin-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 319);

2-[6-amino-9-(tetrahydrofuran-2-ylmethyl)-9*H*-purin-8-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 320);

2-(6-tetrahydrofuran-2-ylmethyl)amino-7*H*-purin-8-ylmethyl-1*H*-benzoimidazole-5-carboxamidine (Compound 321);

2-(1*H*-benzoimidazol-2-ylmethyl)-3-[2-(2-hydroxyethoxy)ethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 322); and

N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-6-fluoro-1*H*-benzoimidazol-4-yloxy]ethyl}acetamide (Compound 323).

EXAMPLE 12

3-(2-aminoethyl)-2-(1*H*-benzoimidazol-2-ylmethyl)-*N*-hydroxy-3*H*-benzoimidazole-5-carboxamidine

(Compound 231),

a prodrug derivative of a compound of Formula I in which A together with B comprises 5-(*N*-hydroxyamidino)-1*H*-benzoimidazol-2-yl, C comprises 3-(2-aminoethyl)-

1H-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture comprising 3-methoxy-4-nitrobenzoic acid (42.0 g, 213 mmol) and thionyl chloride (75 mL, 122.3 g, 1.03 mole) was heated at reflux for 90 minutes, cooled to ambient temperature, concentrated by short-path distillation and cooled to provide a precipitate. The precipitate was isolated and dried to provide 3-methoxy-4-nitrobenzoyl chloride (45.9 g, quantitative) as a light tan solid.

A solution of the 3-methoxy-4-nitrobenzoyl chloride in methylene chloride (300 mL) was cooled to 0 °C and a mixture of *tert*-butyl amine (26.9 mL, 256 mmol, 1.2 equiv), triethylamine (35.7 mL, 256 mmol, 1.2 equiv) and methylene chloride (100 mL) was added dropwise. The mixture was warmed to ambient temperature, concentrated to a slurry and partitioned between ethyl acetate and water. The organic layers were separated, dried (anhydrous sodium sulfate) and concentrated to provide *N-tert*-butyl-3-methoxy-4-nitrobenzamide (51.5 g, 204 mmol) as an off-white solid.

The *N-tert*-butyl-3-methoxy-4-nitrobenzamide and sodium chloride (60.0g) was dissolved in 1,2-dichloroethane (250 mL) and then $POCl_3$ (12.45 mL, 0.134 mol, 1.1 equiv) was added dropwise to the solution at ambient temperature and under an atmosphere of nitrogen. The mixture was heated at reflux for 18 hours, then cooled to ambient temperature and poured onto a 1:1 mixture of methylene chloride and ice (200 mL each). The organic layer was separated and washed with aqueous saturated $NaHCO_3$ solution (3x), dried (anhydrous $MgSO_4$) and concentrated to provide 3-methoxy-4-nitrobenzonitrile (20.6 g, 0.117 mol) as a dark tan solid.

The 3-methoxy-4-nitrobenzonitrile (55.0 g, 309 mmol, 1 equiv) was dissolved in dimethyl sulfoxide (150 mL) and then ethanolamine (21.4 mL, 355 mmol, 1.15 eq) was added to the solution. The mixture was heated at 80 °C for 4 hours, cooled to ambient temperature and poured onto ice/brine to give an orange/red precipitate. The precipitate was collected, washed with water and dried to provide 3-(2-hydroxyethylamino)-4-nitrobenzonitrile (54.1 g, 262 mmol) as a red solid.

A mixture comprising 3-(2-hydroxyethylamino)-4-nitrobenzonitrile (30.2 g, 146 mmol, 1 eq), phthalimide (23.6 g, 160 mmol, 1.1 eq), triphenylphosphine (42.1 g, 160 mmol, 1.1 eq) and anhydrous THF (500 mL) under an atmosphere of nitrogen was cooled to 0 °C and then diethyl azodicarboxylate (25.2 mL, 0.16 mol, 1.1 eq) was added. The reaction was allowed to proceed 30 minutes and then the mixture was poured onto diethyl ether (1 L) to give a precipitate. The precipitate was isolated and dried to provide 3-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethylamino]-4-nitrobenzonitrile (39.3 g, 117 mmol) as a yellow solid.

A biphasic mixture comprising 3-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethylamino]-4-nitrobenzonitrile (38.5 g, 114 mmol, 1 eq), $Na_2S_2O_4$ (119.6 g, 689 mmol, 6 equiv), water (600 Ml) and THF (600 mL) was stirred vigorously at ambient temperature for 1 hour. The organic layer was separated and concentrated to near dryness. The residue was suspended in saturated aqueous $NaHCO_3$ solution and the suspension was stirred for 20 minutes. The solid material in the suspension was isolated by filtration, washed with water and dried to provide 4-amino-3-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethylamino]benzonitrile (29.7 g, 97.0 mmol) as a tan solid.

A solution comprising 4-amino-3-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethylamino]benzonitrile (6.50 g, 21.0 mmol, 1 eq) in acetic acid (250 mL) was warmed to 80 °C and ethyl ethoxycarbonimidoylacetate hydrochloride (7.26 g, 370 mmol, 1.75 eq) was added. The reaction was allowed to proceed 3 hours and then the mixture was concentrated to 75 mL, diluted with water (250 mL), basified with NH_4OH to pH 10 and extracted ethyl acetate. The extract was dried (anhydrous sodium sulfate), filtered, concentrated to a slurry and poured onto diethyl ether (300 mL) to give a precipitate. The precipitate was collected and dried to provide ethyl 6-cyano-1-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethyl]-1*H*-benzoimidazol-2-ylacetate (6.04 g, 15 mmol) as a tan solid.

A mixture comprising ethyl 6-cyano--[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethyl]-1*H*-benzoimidazol-2-ylacetate (5.0 g, 12.43 mmole, 1 eq) and benzene-1,2-diamine (1.88 g, 17.4 mmol, 1.4 eq) was heated at 180 °C in a sealed tube for 3 hours. The mixture was cooled to ambient temperature to give a precipitate. The precipitate was recrystallized from acetonitrile to provide 2-(1*H*-benzoimidazol-2-ylmethyl)-3-[2-(1,3-dioxo-

1,3-dihydroisoindol-2-yl)ethyl]-3*H*-benzoimidazole-5-carbonitrile (5.5 g, 12.3 mmol).

A mixture comprising the 2-(1*H*-benzoimidazol-2-ylmethyl)-3-[2-(1,3-dioxo-
3 1,3-dihydroisoindol-2-yl)ethyl]-3*H*-benzoimidazole-5-carbonitrile (5.0 g, 11.2 mmol, 1 eq) and hydrazine monohydrate (2.24 g, 44.8 mmol, 4 eq) was stirred at ambient temperature for 8 hours and then additional hydrazine monohydrate (4 eq) was added. The mixture was
6 stirred for 2 hours and then concentrated under reduced pressure. The residue was dissolved in acetonitrile and 3N hydrochloric acid was added to the solution to give a precipitate. The precipitate was isolated and dried to provide 3-(2-aminoethyl)-
9 2-(1*H*-benzoimidazol-2-ylmethyl)-3*H*-benzoimidazole-5-carbonitrile.

A mixture comprising 3-(2-aminoethyl)-2-(1*H*-benzoimidazol-2-ylmethyl)-3*H*-benzoimidazole-5-carbonitrile (1.34 g, 4.24 mmol), $NaHCO_3$ (2.84 g, 33.9 mmol),
12 hydroxylamine hydrochloride (1.17 g, 16.96 mmol) and ethanol was heated at reflux for 12 hours. The mixture was cooled to ambient temperature to give a precipitate. The precipitate was isolated by filtration, washed numerous times with water and dried *in vacuo*
15 to provide 3-(2-aminoethyl)-2-(1*H*-benzoimidazol-2-ylmethyl)-*N*-hydroxy-3*H*-benzoimidazole-5-carboxamidine (900 mg, 2.7 mmol) as a white powder.

Proceeding as in Example 12, but substituting other starting materials, provided the
18 following compounds of Formula I:

2-(1*H*-benzoimidazol-2-ylmethyl)-*N*-hydroxy-3-[3-(2-oxopyrrolidin-1-yl)propyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 233); and
21 *N*-hydroxy-2-(1-methyl-1*H*-benzoimidazol-2-ylmethyl)-3-[3-(2-oxopyrrolidin-1-yl)propyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 234).

EXAMPLE 13

24 3-(2-Aminoethyl)-2-(1*H*-benzoimidazol-2-ylmethyl)-3*H*-benzoimidazole-5-carboxamidine (Compound 235),

a compound of Formula I in which A together with B comprises 5-amidino-

1*H*-benzoimidazol-2-yl, C comprises 3-(2-aminoethyl)-1H-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture comprising 3-(2-aminoethyl)-2-(1*H*-benzoimidazol-2-ylmethyl)-*N*-hydroxy-3*H*-benzoimidazole-5-carboxamidine (600 mg, 1.8 mmol), zinc (300 mg) and acetic acid (10 mL) was heated at reflux for 3 hours. The mixture was cooled, filtered and concentrated under reduced pressure. The residue was dissolved in 3N hydrochloric acid (20 mL) and the solution was heated at reflux for 3 hours and then concentrated under reduced pressure to provide 3-(2-aminoethyl)-2-(1*H*-benzoimidazol-2-ylmethyl)-3*H*-benzoimidazole-5-carboxamidine (620 mg, 1.4 mmol) as an off-white solid.

Proceeding as in Example 13, but substituting other starting materials, provided the following compounds of Formula I:

2-(1*H*-benzoimidazol-2-ylmethyl)-3-(3-phenylpropyl)-3*H*-benzoimidazole-5-carboxamidine (Compound 236);

4-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidinobenzoimidazol-1-yl]ethoxy}benzoic acid (Compound 237);

2-(1*H*-benzoimidazol-2-ylmethyl)-3-[3-(2-oxopyrrolidin-1-yl)propyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 238);

ethyl 4-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidinobenzoimidazol-1-yl]ethoxy}benzoate (Compound 239); and

2-(1-methyl-1*H*-benzoimidazol-2-ylmethyl)-3-[3-(2-oxopyrrolidin-1-yl)propyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 240);

2-{4-[2-(2,5-dioxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}benzothiazole-6-carboxamidine (Compound 324);

N-{2-[2-(6-amidinobenzothiazol-2-ylmethyl)-6-fluoro-1*H*-benzoimidazol-4-yloxy]ethyl}succinamide (Compound 325);

2-[1-(1*H*-benzoimidazol-2-yl)-1-hydroxy-2-pyridin-3-ylethyl]benzothiazole-6-carboxamidine (Compound 326);

2-[1-(1*H*-benzoimidazol-2-yl)-4-pyridin-4-ylbutyl]benzothiazole-6-carboxamidine (Compound 327);

2-benzothiazol-2-ylmethylbenzothiazole-6-carboxamidine (Compound 328)

N-{4-[4-(1*H*-benzoimidazol-2-yl)-4-(6-amidinobenzothiazol-2-yl)butyl]phenyl}acetamide (Compound 329);

2-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidinobenzothiazol-2-yl)ethyl]phenoxyacetic acid (Compound 330);

2-[1-(1*H*-benzoimidazol-2-yl)-2-(2-fluorophenyl)ethyl]benzothiazole-6-carboxamidine (Compound 331);

2-(4,6-difluoro-1H-benzoimidazol-2-ylmethyl)benzothiazole-6-carboxamidine (Compound 332);

2-{6-fluoro-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}benzothiazole-6-carboxamidine (Compound 333);

3-(1*H*-benzoimidazol-2-yl)-3-(5-amidinobenzothiazol-2-yl)propionate (Compound 334);

2-[1-(1*H*-benzoimidazol-2-yl)-2-pyridin-3-ylethyl]benzothiazole-6-carboxamidine (Compound 335);

ethyl 3-(1*H*-benzoimidazol-2-yl)-3-(5-amidinobenzothiazol-2-yl)propionate (Compound 336);

2-(1-(1*H*-benzoimidazol-2-yl)-2-{4-[2-(2-oxopyrrolidin-1-yl)ethoxy]phenyl}ethyl)benzothiazole-6-carboxamidine (Compound 337);

4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidinobenzothiazol-2-yl)ethyl]phenoxyacetic acid (Compound 338);

2-(1-(1*H*-benzoimidazol-2-yl)-2-{4-[2-(2,5-dioxopyrrolidin-1-yl)ethoxy]phenyl}ethyl)benzothiazole-6-carboxamidine (Compound 339);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(2-morpholin-4-ylethoxy)phenyl]ethyl}benzothiazole-6-carboxamidine (Compound 340);

N-{2-[2-(6-amindinobenzothiazol-2-ylmethyl)-3*H*-benzoimidazol-1-yl]ethyl}acetamide (Compound 341);

3-(1*H*-benzoimidazol-2-yl)-*N*-benzyl-3-(5-amidinobenzothiazol-2-yl)propionamide (Compound 342);

2-[1-(1*H*-benzoimidazol-2-yl)-3-(4-benzylpiperazin-1-yl)-3-oxopropyl]benzothiazole-6-carboxamidine (Compound 343);

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]benzothiazole-6-carboxamidine (Compound 344);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(2-morpholin-4-yl-2-oxoethoxy)phenyl]ethyl}benzothiazole-6-carboxamidine (Compound 345);

2-{3-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidinobenzothiazol-2-yl)ethyl]phenoxy}-*N*-tetrahydrofuran-2-ylmethylacetamide (Compound 336);

2-{4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidinobenzothiazol-2-yl)ethyl]phenoxy}-*N*-tetrahydrofuran-2-ylmethylacetamide (Compound 337);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[3-(2-morpholin-4-yl-2-oxoethoxy)phenyl]ethyl}benzothiazole-6-carboxamidine (Compound 338);

2-[1-(1*H*-benzoimidazol-2-yl)-3-morpholin-4-yl-3-oxopropyl]benzothiazole-6-carboxamidine (Compound 339);

2-{6-fluoro-4-[2-(1-methylpyrrolidin-2-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}benzothiazole-6-carboxamidine (Compound 340);

2-[1-(1*H*-benzoimidazol-2-yl)-2-piperidin-3-ylethyl]benzothiazole-6-carboxamidine (Compound 341);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(pyrrolidin-3-yloxy)phenyl]ethyl}benzothiazole-6-carboxamidine (Compound 342);

2-(1-(1*H*-benzoimidazol-2-yl)-2-{4-[2-(4-hydroxypiperidin-1-yl)-2-oxoethoxy]phenyl}ethyl)benzothiazole-6-carboxamidine (Compound 343); and

N-[2-(6-amidinobenzothiazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]acetamide (Compound 344).

EXAMPLE 14

N-{2-[2-(5-Amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}-
3 2-(*p*-tolylsulfonylamino)acetamide
(Compound 241),
a compound of Formula I in which A together with B comprises 5-amidino-
6 1*H*-benzoimidazol-2-yl, C comprises 1-[2-(*p*-tolylsulfonylaminoacetylamino)ethyl]-
1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture comprising 2-[1-(2-aminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-
9 1*H*-benzoimidazole-5-carboxamidine (250 mg, 0.615 mmol, 1 eq), dimethyl formamide (3 mL), *N*,*N*-diisopropylethylamine (0.21 mL, 159 mg, 1.23 mmol, 2 eq) and 1,1-carbonyldiimidazole acid (125 mg, 0.77 mmol, 1.25 eq) was stirred for 5 minutes and
12 then *N*-(*p*-tolylsulfonyl)aminoacetic (177 mg, 0.77mmol, 1.25 eq) was added. The mixture was stirred at ambient temperature for 12 hours and then poured into diethyl ether to give a precipitate. The precipitate was isolated by decanting off the solvents and dissolved in 1N
15 hydrochloric acid (20 mL). The solution was lyophilized and the residue was purified using reverse-phase C-18 HPLC (2-35% gradient
acetonitrile in 40 mmolar hydrochloric acid) to provide *N*-{2-[2-(5-amidino-
18 1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}-
2-(*p*-tolylsulfonylamino)acetamide (150 mg, 0.277 mmol) as a yellow solid.

Proceeding as in Example 14, but substituting other starting materials, provided the
21 following compounds of Formula I:

N-{2-[2-(5-amidino-
1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}succinamic acid (Compound 242);
24 2-[4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-
1*H*-benzoimidazole-5-carboxamidine (Compound 243);
N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-
27 5-fluorobenzoimidazol-1-yl]ethyl}acetamide (Compound 244), MS (BIOION), Calculated

for $C_{20}H_{20}FN_8O$: MH^-: 393.17; Found: MH^+: 394.1;

N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-

6-fluorobenzoimidazol-1-yl]ethyl}acetamide (Compound 245), MS (BIOION), Calculated for $C_{20}H_{20}FN_8O$: MH^-: 393.17; Found: MH^+: 394.2;

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-

3*H*-benzoimidazol-5-ylmethyl]acetamide (Compound 246);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-3-cyclohexylpropionamide (Compound 247);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-

1*H*-benzoimidazol-5-ylmethyl]hexanamide (Compound 248);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-

4-phenylbutyramide (Compound 249);

N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}-3-piperidin-1-ylpropionamide (Compound 250);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-2-(2,5-dioxoimidazolidin-4-yl)acetamide (Compound 251);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-

2-(pyridin-4-ylsulfanyl)acetamide (Compound 252);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-2-methoxyacetamide (Compound 253);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-2-phenoxyacetamide (Compound 254);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-

6-methylpyrazine-2-carboxamide (Compound 255);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-

6-amidinobenzoimidazol-1-yl]ethyl}acetamide (Compound 256);

N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}hexanamide (Compound 257);

2-benzo[1,3]dioxol-5-yl-*N*-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-

1*H*-benzoimidazol-5-ylmethyl]acetamide (Compound 258);

N-{2-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}-3-methoxypropionamide (Compound 259);

N-{2-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}-2-(2-oxoimidazolidin-4-yl)acetamide (Compound 260);

2-benzo[1,3]dioxol-5-yl-*N*-{2-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}acetamide (Compound 261);

N-{2-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}-4-trifluoromethoxybenzamide (Compound 262);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}-2-methoxybenzamide (Compound 263);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}-2-methoxyacetamide (Compound 264);

2-benzo[1,3]dioxol-5-yl-*N*-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}acetamide (Compound 265);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}-2-(2,5-dioxoimidazolidin-4-yl)acetamide (Compound 266);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}tetrahydrofuran-3-carboxamide (Compound 267);

3-phenylsulfonyl-*N*-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}propionamide (Compound 268);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}-2-*p*-tolylsulfonylaminoacetamide (Compound 269);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-2-*p*-tolylsulfonylaminoacetamide (Compound 270);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-4-trifluoromethoxybenzamide (Compound 271);

N-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-3-methoxypropionamide (Compound 272);

N-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethyl]-

4-cyanobenzamide (Compound 273);

N-{2-[2-(6-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethyl}-2-(pyridin-4-ylsulfanyl)acetamide (Compound 274);

N-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}-5-methylpyrazine-2-carboxamide (Compound 275);

2-phenylsulfonyl-*N*-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-benzoimidazol-1-yl]ethyl}acetamide (Compound 276);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidinobenzoimidazol-1-yl]ethyl}-2-phenoxyacetamide (Compound 277);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidinobenzoimidazol-1-yl]ethyl}-3-cyclohexylpropionamide (Compound 278); and

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidinobenzoimidazol-1-yl]ethyl}-4-phenylbutyramide (Compound 279).

EXAMPLE 15

2-{1-[2-(3,5-Dimethyl-2,3-dihydroisoxazole-4-sulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 280),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl, C comprises 1-[2-(3,5-dimethyl-2,3-dihydroisoxazole-4-sulfonylamino)ethyl]-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture of 2-[1-(2-aminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (250 mg, 0.615 mmol, 1 eq), dimethyl formamide (2 mL), *N*,*N*-diisopropylethylamine (0.21 mL, 159 mg, 1.23 mmol, 2 eq) and 3,5-dimethylisoxazole-4-sulphonyl chloride (148 mg, 0.76 mmol, 1.25 eq) was stirred at ambient temperature for 12 hours.

The mixture was poured into a 1:1 solution of diethyl ether and acetonitrile to give a precipitate. The precipitate was isolated by decanting of the solvents and dissolved in 1N hydrochloric acid (20 mL). The solution was lyophilized and the residue was purified using

reverse-phase C-18 HPLC (2-50% gradient acetonitrile in 40mM hydrochloric acid) to provide 2-{1-[2-(3,5-dimethyl-2,3-dihydroisoxazole-4-sulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine as a yellow solid, MS (BIOION), Calculated for $C_{23}H_{24}N_9SO_3$: MH^+: 492.7; Found: MH^+: 494.9.

Proceeding as in Example 15, but substituting other starting materials, provided the following compounds of Formula I:

2-{1-[2-(naphthalen-1-ylsulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 281), MS (BIOION), Calculated for $C_{28}H_{25}N_8SO_2$: MH^+: 523.18; Found: MH^+: 524.4;

2-{1-[2-(quinolin-8-ylsulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 282), MS (BIOION), Calculated for $C_{27}H_{24}N_9SO_2$: MH^+: 524.17; Found: MH^+: 525.4;

N-(4-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)benzoimidazol-1-yl]ethylsulfamoyl}thiazol-2-yl)acetamide (Compound 283), MS (BIOION), Calculated for $C_{24}H_{26}N_9SO_3$: MH^+: 551.64; Found: MH^+: 552.3;

2-{1-[2-(7,7-dimethyl-2-oxobicyclo[2.2.1]hept-1-ylsulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 284), MS (BIOION), Calculated for $C_{27}H_{31}N_8SO_3$: MH^+: 533.22; Found: MH^+: 534.2;

2-[1-(2-benzylsulfonylaminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 285), MS (BIOION), Calculated for $C_{25}H_{25}N_8SO_2$: MH^+: 487.18; Found: MH^+: 488.1;

2-[1-(2-ethylsulfonylaminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 286), MS (BIOION), Calculated for $C_{20}H_{23}N_8SO_2$: MH^+: 425.16; Found: MH^+: 426.3;

4-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-benzoimidazol-1-yl]ethylsulfamoyl}benzoic acid (Compound 287), MS (BIOION), Calculated for $C_{25}H_{23}N_8SO_4$: MH^+: 517.15; Found: MH^+: 518.2;

2-(5-naphthalen-1-ylsulfonylaminomethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 288);

2-(5-naphthalen-2-ylsulfonylaminomethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 289);

2-[5-(*p*-tolylsulfonylaminomethyl)-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 290);

2-[5-(5-dimethylaminonaphthalen-1-ylsulfonylaminomethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 291);

3-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethylsulfamoyl]benzoic acid (Compound 292);

4-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazol-5-ylmethylsulfamoyl]benzoic acid (Compound 293);

2-[5-(phenylsulfonylaminomethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 294);

2-(5-dimethylsulfamoylaminomethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 295);

2-[1-(2-dimethylsulfamoylaminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 296), MS (ESI), Calculated for $C_{20}H_{24}N_9SO_2$: MH^+: 440.17; Found: MH^+: 441.1;

2-[5-(3-methylisoxazol-4-ylsulfonylaminomethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 297);

2-(5-ethylsulfonylaminomethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 298);

2-{1-[2-(naphthalen-2-ylsulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 299);

2-{1-[2-(3,5-dimethylisoxazole-4-sulfonylamino)ethyl]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 300);

2-{1-[2-(3,5-dimethylisoxazole-4-sulfonylamino)ethyl]-5-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 301);

N-{2-[2-(1*H*-benzoimidazol-2-ylmethyl)-6-amidino-3*H*-benzoimidazol-1-yl]ethyl}-

3-*p*-tolylsulfonylaminopropionamide (Compound 302); and

2-(1*H*-benzoimidazol-2-ylmethyl)-3-(2-naphthalen-2-ylsulfonylaminoethyl)-3*H*-benzoimidazole-5-carboxamidine (Compound 303).

EXAMPLE 16

2-{1-[2-(1*H*-Imidazol-2-ylmethylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-3*H*-benzoimidazole-5-carboxamidine

(Compound 304),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl, C comprises 1-[2-(1*H*-Imidazol-2-ylmethylamino)ethyl]-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$

A mixture comprising 2-[1-(2-aminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (250 mg, 0.615 mmol, 1 eq), methanol (5 mL), Na_2CO_3 (65 mg, 0.615 mmol, 1 eq) and 1*H*-imidazole-2-carboxaldehyde (63 mg, 0.646 mmol, 1.05 eq) was stirred for 5 minutes and then sodium cyanoborohydride (41 mg, 0.646 mmol, 1.05 eq) was added. The mixture was acidified with glacial acetic acid added dropwise, stirred at ambient temperature for 12 hours, filtered and poured into diethyl ether to give a precipitate. The precipitate was isolated and dissolved in 1N hydrochloric acid (10 mL). The solution was lyophilized and the residue was purified using reverse-phase C-18 HPLC (2-17% gradient acetonitrile in 40mM hydrochloric acid) to provide 2-{1-[2-(1*H*-imidazol-2-ylmethylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-3*H*-benzoimidazole-5-carboxamidine as a yellow solid.

Proceeding as in Example 16, but substituting other starting materials, provided the following compounds of Formula I:

2-(1-{2-[(8-hydroxyquinolin-2-ylmethyl)amino]ethyl}-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 305), MS (BIOION), Calculated for $C_{28}H_{26}N_9O$: MH^+: 490.22; Found: MH^+: 491.3; and

2-[1-(2-pyridin-2-ylmethylaminoethyl)-1*H*-benzoimidazol-2-ylmethyl)-

3*H*-benzoimidazole-5-carboxamidine (Compound 306).

EXAMPLE 17

2-(5-Aminomethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 307),

a compound of Formula I in which A together with B comprises 5-amidino-1*H*-benzoimidazol-2-yl, C comprises 5-aminomethyl-1*H*-benzoimidazol-2-yl and X^3 is $-CH_2-$

A solution comprising *N*-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-3*H*-benzoimidazol-5-ylmethyl]acetamide (6.18 g, 14 mmol) in 6 M hydrochloric acid (50 mL) was heated at reflux for 1 hour, cooled and lyophilized. The residue was purified by preparatory HPLC to provide 2-(5-aminomethyl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine, MS (ESI), Calculated for $C_{17}H_{17}N_8$: MH^+: 319.4, Found: MH^+: 319.9.

Proceeding as in Example 17, but substituting other starting materials, provided the following compound of Formula I:

2-[1-(2-aminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 308).

Proceeding by the methods described in this Application provided the following compounds of Formula I:

2-[1-(6-aminomethyl-1*H*-benzoimidazol-2-yl)-2-(4-methoxyphenyl)ethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 345);

2-[1-(1*H*-benzoimidazol-2-yl)-2-(4-benzyloxyphenyl)ethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 346);

2-[1-(1*H*-benzoimidazol-2-yl)-2-pyridin-4-ylethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 347);

2-[1-(1*H*-benzoimidazol-2-yl)-2-piperidin-4-ylethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 348);

2-[1-(1*H*-benzoimidazol-2-yl)-2-(1-naphthalen-2-ylsulfonylpiperidin-4-yl)ethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 349);

2-[1-(1*H*-benzoimidazol-2-yl)-2-(1-toluen-4-ylsulfonylpiperidin-4-yl)ethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 350);

2-[1-(1*H*-benzoimidazol-2-yl)-2-(1-dimethylsulfamoylpiperidin-4-yl)ethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 351);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[3-(4-fluorobenzyloxy)phenyl]ethyl}-3*H*-benzoimidazole-5-carboxamidine (Compound 352);

2-[1-(1*H*-benzoimidazol-2-yl)-4-phenylbutyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 353);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(4-benzylpiperazin-1-ylcarbonyl)phenyl]ethyl}-3*H*-benzoimidazole-5-carboxamidine (Compound 354);

2-[1-(1*H*-benzoimidazol-2-yl)-4-(4-hydroxy-3-methoxyphenyl)butyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 355);

4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-*N*-pyridin-3-ylmethylbenzamide (Compound 356);

N-(2-{4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]piperidin-1ylsulfonyl}-5-methylthiazol-4-yl)acetamide (Compound 357);

ethyl 4-[4-(1*H*-benzoimidazol-2-yl)-4-(5-amidino-1*H*-benzoimidazol-2-yl)butyl]-2-methoxyphenoxyacetate (Compound 358);

2-[1-(1*H*-benzoimidazol-2-yl)-4-(4-dimethylaminophenyl)butyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 359);

methyl 4-{4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-5-methylimidazol-1-ylmethyl}benzoate (Compound 360);

5-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]furan-2-carboxylic acid (Compound 361);

4-[4-(1*H*-benzoimidazol-2-yl)-4-(5-amidino-1*H*-benzoimidazol-2-yl)butyl]-2-methoxyphenoxyacetic acid (Compound 362);

3-{4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]phenoxymethyl}benzoic acid (Compound 363);

2-[1-(1*H*-benzoimidazol-2-yl)-2-(1-benzylsulfonylpiperidin-4-yl)ethyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 364);

4-{4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-5-methylimidazol-1-ylmethyl}benzoic acid (Compound 365);

3-{4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-5-methylimidazol-1-ylmethyl}benzoic acid (Compound 366);

2-[4-(4-aminophenyl)-1-(1*H*-benzoimidazol-2-yl)butyl]-3*H*-benzoimidazole-5-carboxamidine (Compound 367);

4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-*N*-pyridin-3-ylmethylbenzamide (Compound 368);

N-(2-acetylaminoethyl)-5-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]furan-2-carboxamide (Compound 369);

5-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-*N*-pyridin-4-ylmethylfuran-2-carboxamide (Compound 370);

5-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-*N*-pyridin-3-ylmethylfuran-2-carboxamide (Compound 371);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(3-hydroxypyrrolidin-1-ylcarbonyl)phenyl]ethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 372);

3-{4-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]benzoylsulfonyl}benzoic acid (Compound 373);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(3-dimethylaminopropoxy) phenyl] ethyl}-3*H*-benzoimidazole-5-carboxamidine (Compound 374);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(4-methylpiperazin-1-ylcarbonyl)phenyl]ethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 375);

3-[2-(5-amidino-1*H*-benzoimidazol-2-yl)-2-(1*H*-benzoimidazol-2-yl)ethyl]benzoic

acid (Compound 376);

3-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-*N*-[2-(4-sulfamoylphenyl)ethyl]benzamide (Compound 377);

2-(1-(1*H*-benzoimidazol-2-yl)-2-{4-[4-(2-hydroxyethyl)piperazin-1-ylcarbonyl]phenyl}ethyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 378);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[3-(4-phenylpiperazin-1-ylcarbonyl)phenyl]ethyl}-1*H*-benzoimidazole-5-carboxamidine (Compound 379);

3-[2-(1*H*-benzoimidazol-2-yl)-2-(5-amidino-1*H*-benzoimidazol-2-yl)ethyl]-*N*-(2-hydroxy-1-hydroxymethylethyl)benzamide (Compound 380);

2-[2-(4-aminophenyl)-1-(1*H*-benzoimidazol-2-yl)ethyl]-1*H*-benzoimidazole-5-carboxamidine (Compound 381);

2-(1-{4-[2-(2,5-dioxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-yl}-4-phenylbutyl)-1*H*-benzoimidazole-5-carboxamidine (Compound 382);

2-{1-(1*H*-benzoimidazol-2-yl)-2-[4-(3-dimethylaminopropoxy)phenyl]ethyl}-3*H*-benzoimidazole-5-carboxamidine (Compound 383); and

3-(5-amidino-1*H*-benzoimidazol-2-yl)-3-{4-[2-(2,5-dioxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-yl}-2-oxopropionic acid (Compound 384);

EXAMPLE 18

In Vitro Enzyme Inhibitor Assay

Mixtures of human Factor Xa (0.5-5 nM) and test compound (varying concentrations) in assay medium (comprising: Tris, 50 mM (pH 8); NaCl, 1M; $CaCl_2$, 5 mM; polyoxyethylenesorbitan monolaurate (Tween-20), 0.05%; DMSO, 10%; and zinc chloride, 150μM) were incubated for 1 hour at room temperature and then substrate, MesOC-Norleu-Gly-Arg-pNA, was added such that the final concentration of the substrate in the assay mixture was between 0.5 and 5 mM. Hydrolysis of the substrate was followed spectrophotometrically at (405 λ) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Proceeding as described in Example 18 or by methods known to those of ordinary skill the following compounds of the invention were tested for factor Xa inhibitory activity:

Compound 1, K_i=0.0008μM; Compound 34, K_i=0.0006μM; Compound 60, K_i=0.001μM; Compound 90, K_i=0.006μM; Compound 101, K_i=0.0006μM; Compound 105, K_i=0.005μM; Compound 107, K_i=0.002μM; Compound 134, K_i=0.0007μM; Compound 138, K_i=0.02μM; Compound 143, K_i=0.004μM; Compound 150, K_i=0.003μM; Compound 154, K_i=0.0007μM; Compound 155, K_i=0.05μM; Compound 156, K_i=0.004μM; Compound 157, K_i=1.4μM; Compound 162, K_i=0.009μM; Compound 165, K_i=0.005μM; Compound 185, K_i=0.002μM; Compound 187, K_i=0.01μM; Compound 189, K_i=0.003μM; Compound 192, K_i=0.004μM; Compound 193, K_i=0.004μM; Compound 194, K_i=0.0035μM; Compound 207, K_i=0.004μM; Compound 208, K_i=0.006μM; Compound 211, K_i=7μM; Compound 212, K_i=0.02μM; Compound 213, K_i=0.007μM; Compound 214, K_i=0.003μM; Compound 215, K_i=0.005μM; Compound 216, K_i=0.004μM; Compound 219, K_i=0.002μM; Compound 222, K_i=0.004μM; Compound 280, K_i=0.04μM; Compound 285, K_i=0.001μM; Compound 299, K_i=0.007μM; Compound 312, K_i=0.07μM; Compound 314, K_i=0.04μM; and Compound 323, K_i=0.003μM.

EXAMPLE 19

Ex vivo ACT Assay

Rabbits were sedated with Hypnorm® (fluanisone 10 mg/mL and phentanylcitrate 0.315 mg/mL; 0.05 mL/kg, i.m.). A catheter (Venflon®2, ⌀ 0.8/25 mm) was inserted into a marginal ear vein for adminstration of test compound. A second catheter (Venflon®2, ⌀ 1.0/32 mm) was inserted into the artery of the other ear for blood sampling. Test compounds were administered by i.v. bolus injection. Blood samples were collected (0.5 mL) prior to adminstration of test compounds and at various time points thereafter.

The activating clotting time (ACT), the amount of time for clot formation, was measured with a Medtronic Automated Coagulation Timer ACT II. An aliquot (200 μL) of

the blood sample was added to each of two reaction chambers of a disposable two-channel test cartridge containing assay buffer (comprising: 0.75% kaolin, as the activator, and 0.0025M $CaCl_2$ in 0.1 mL HEPES buffer for non-citrated blood and 2.2% kaolin and 0.05M $CaCl_2$ in 0.1 mL HEPES buffer for citrated blood). Clot formation was measured as a decrease in the downward motion of a plunger assembly contained by the test cartridge. The decrease in downward motion of the plunger was detected by a photo-optic system. The concentration of test compounds necessary to double ACT was determined.

Proceeding as described in Example 19, compounds of the present Invention were assayed and found to increase.

EXAMPLE 20

In vitro ACT Assay

Rabbit blood was collected from an indwelling catheter in a ear artery into plastic containers. Human blood was collected via venipuncture into vacutainers, some of which contained 0.5 mL of 3.8% citrate. ACT was measured as described in Example 19. Blood samples were mixed with varying concentrations of test compounds dissolved in physiological saline (30μL for non-citrated blood and 15μL for citrated blood). Non-citrated blood was used in the assay immediately upon its collection. Citrated blood was kept at ambient temperature for 0.5 to 2 hours and then incubated at 37 °C before used. The concentration of test compounds necessary to effect a doubling of the ACT (EC_{X2}) was determined.

Proceeding as described in Example 20, compounds of the present Invention were assayed and found to have the following EC_{X2} values:

Compound 34, $EC_{X2rabbit}$= 49μM, $EC_{X2human}$= 34μM, 44μM;

Compound 60, $EC_{X2rabbit}$= 13μM, $EC_{X2human}$= 24μM, 28μM;

Compound 90, $EC_{X2rabbit}$= 43μM; Compound 101, $EC_{X2rabbit}$= 41μM;

Compound 105, $EC_{X2rabbit}$= 49μM; Compound 107, $EC_{X2rabbit}$= 47μM;
Compound 134, $EC_{X2human}$= 41μM, 44μM; Compound 138, $EC_{X2human}$= 49μM;
Compound 143, $EC_{X2rabbit}$= 24μM, $EC_{X2human}$= 20μM, 25μM;
Compound 150, $EC_{X2rabbit}$= 24μM, $EC_{X2human}$= 26μM, 28μM;
Compound 154, $EC_{X2rabbit}$= 35μM, $EC_{X2human}$= 26μM, 34μM;
Compound 155, $EC_{X2rabbit}$= 26μM, $EC_{X2human}$= 15μM; Compound 156, $EC_{X2rabbit}$= 39μM,

$EC_{X2human}$= 35μM; Compound 157, $EC_{X2rabbit}$= 45μM, $EC_{X2human}$= 29μM;
Compound 162, $EC_{X2rabbit}$= 24μM, $EC_{X2human}$= 36μM; Compound 165, $EC_{X2rabbit}$= 34μM;
Compound 185, $EC_{X2rabbit}$= 26μM, $EC_{X2human}$= 19μM; Compound 187, $EC_{X2human}$= 41μM;
Compound 189, $EC_{X2rabbit}$= 16μM, $EC_{X2human}$= 16μM, 18μM;
Compound 192, $EC_{X2rabbit}$= 42μM, $EC_{X2human}$= 28μM; Compound 193, $EC_{X2rabbit}$= 13μM,
$EC_{X2human}$= 21μM; Compound 194, $EC_{X2rabbit}$= 10μM, $EC_{X2human}$= 8μM, 12μM;
Compound 207, $EC_{X2rabbit}$= 14μM, $EC_{X2human}$= 18μM, 28μM;
Compound 208, $EC_{X2rabbit}$= 38μM; Compound 211, $EC_{X2rabbit}$= 47μM, $EC_{X2human}$= 43μM;
Compound 212, $EC_{X2rabbit}$= 39μM, $EC_{X2human}$= 28μM; Compound 213, $EC_{X2rabbit}$= 44μM,
$EC_{X2human}$= 20μM; Compound 214, $EC_{X2rabbit}$= 47μM, $EC_{X2human}$= 22μM;
Compound 215, $EC_{X2rabbit}$= 8μM, $EC_{X2human}$= 9μM; Compound 216, $EC_{X2rabbit}$= 19μM,
$EC_{X2human}$= 19; Compound 219, $EC_{X2rabbit}$= 8μM, $EC_{X2human}$= 17μM;
Compound 222, $EC_{X2rabbit}$= 36μM; Compound 280, $EC_{X2human}$= 24μM;
Compound 285, $EC_{X2human}$= 38μM; Compound 299, $EC_{X2human}$= 31μM;
Compound 312, $EC_{X2human}$= 27μM; Compound 314, $EC_{X2rabbit}$= 23μM, $EC_{X2human}$= 48μM; and
Compound 323, $EC_{X2rabbit}$= 23μM, $EC_{X2human}$= 29μM.

EXAMPLE 21

The following are representative pharmaceutical formulations containing a compound of Formula I.

ORAL FORMULATION

Compound of Formula I	10-100 mg
Citric Acid Monohydrate	105 mg
Sodium Hydroxide	18 mg
Flavoring	
Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

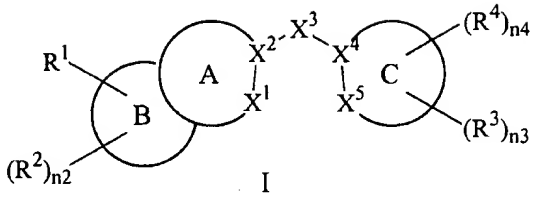
Compound of Formula I	0.1-10 mg
Dextrose Monohydrate	q.s. to make isotonic
Citric Acid Monohydrate	1.05 mg
Sodium Hydroxide	0.18 mg
Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

Compound of Formula I	1%
Microcrystalline Cellulose	73%
Stearic Acid	25%
Colloidal Silica	1%.

WE CLAIM:

1. A compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from -N=, $-NR^5-$, -O- and -S-, wherein R^5 is $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and X^5 is a heteroatom moiety selected from -N=, $-NR^5-$, -O- and -S-, wherein R^5 is as defined above, and any carbocyclic ketone, thioketone and iminoketone derivative thereof;

X^3 is -O-, -S-, -C(O)-, $-NR^7-$, $-SiR^7R^8-$ or $-CR^7R^8-$, wherein R^7 is hydrogen, (C_{1-6})alkyl or hydroxy and R^8 is $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, or R^7 and/or R^8 together with a free valence on the annular atom adjacent to X^4 forms (C_3)alkylene;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any annular atom with an available valence comprising B;

each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from (C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo, hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; with the proviso that R^2, R^3, R^4, R^5, R^7 and R^8 are not all hydrogen and/or (C_{1-3})alkyl when A together with B comprises 1*H*-benzoimidazol-2yl, C comprises 1*H*-benzoimidazol-2yl and X^3 is $-CR^7R^8-$; and

the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

2. The compound of Claim 1 in which:

n2 is 1;

A together with B comprises a fused heterobicyclic radical containing 8 to 10 annular atoms, wherein each ring contains 5 to 6 annular members;

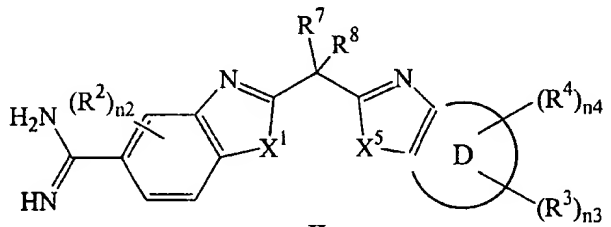
C comprises a heteromonocyclic or fused heteropolycyclic radical containing from 8 to 18 annular atoms, wherein each ring contains 5 to 6 annular atoms;

X^3 is $-C(O)-$, $-NR^7-$ or $-CR^7R^8-$;

R^2 is hydrogen, (C_{1-3})alkyl or halo;

each R^3 is independently hydrogen, cyano, halo, nitro or perhalo(C_{1-3})alkyl; and each R^4, R^5 and R^8 is independently $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 10 contiguous linking atoms and R^6 is hydrogen, (C_{6-10})aryl, cyclo(C_{3-6})alkyl, hetero(C_{5-10})aryl, heterocyclo(C_{5-6})alkyl or hetero(C_{8-10})polycycloaryl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

3. The compound of Claim 2 which is a compound of Formula II:



II

in which D together with the vinylene moiety to which it is fused comprises a monocyclic or hetermonocyclic divalent radical containing 6 annular atoms; and X^1 and X^5 are independently a heteroatom moiety selected from $-NR^5-$, $-O-$ and $-S-$; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

4. The compound of Claim 3 in which each R^4, R^5 and/or R^8 is independently $-R^6$, wherein R^6 is (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl, or $-X^6-R^6$, wherein X^6 is (C_{1-10})alkylene or (C_{2-10})heteroalkylene and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

5. The compound of Claim 3 in which each R^3 is independently cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and/or each R^4 is independently hydroxy, mercapto, sulfo, $-NHR^9$ or $-OP(O)(OR^9)OH$, wherein R^9 is hydrogen or (C_{1-6})alkyl; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

6. The compound of Claim 3 in which one of X^1 and X^5 is $-NR^5-$ and the other is a heteroatom selected from –O– and –S–; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

7. The compound of Claim 3 in which X^1 is –S– and X^5 is $-NR^5-$; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

8. The compound of Claim 4 selected from:

2-{4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(2-hydroxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-(5-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-methoxyethoxy)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[5-(2-amino-2,3-dihydroimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-oxopyrrolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(2,5-dioxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-oxoimidazolidin-1-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-(4-benzo[1,3]dioxol-5-ylmethoxy-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

(*S*)-2-[6-fluoro-4-(5-oxopyrrolidin-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-(4,6-diimidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(1-azabicyclo[2.2.2]oct-3-yloxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-(6-fluoro-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-{7'-[2-(2-oxopyrrolidin-1-yl)ethoxy]-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-isopropylimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(tetrahydrofuran-2-ylmethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-methylimidazol-1-yl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[6-fluoro-4-(2-pyrrolidin-1-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(2-dimethylaminoethoxy)-6-fluoro-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-(6-ethoxy-4-imidazol-1-yl-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-(6-fluoro-4-tetrahydropyran-2-ylmethoxy-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(2-oxooxazolidin-3-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(3,3-dimethyl-2-oxopyrrolidin-1-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{4-[2-(1,3-dioxooctahydroisoindol-2-yl)ethoxy]-6-fluoro-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-{6-fluoro-4-[2-(1-methylpyrrolidin-2-yl)ethoxy]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[4-(2-morpholin-4-ylethoxy)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{1-[2-(3,5-dimethyl-2,3-dihydroisoxazole-4-sulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-[1-(2-benzylsulfonylaminoethyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine;

2-{1-[2-(naphthalen-2-ylsulfonylamino)ethyl]-1*H*-benzoimidazol-2-ylmethyl}-1*H*-benzoimidazole-5-carboxamidine;

2-(7'-ethoxy-3'*H*-[1,5']bibenzoimidazolyl-2'-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine;

2-[6-chloro-4-(2-piperidin-1-ylethylsulfamoyl)-1*H*-benzoimidazol-2-ylmethyl]-1*H*-benzoimidazole-5-carboxamidine; and

N-{2-[2-(5-amidino-1*H*-benzoimidazol-2-ylmethyl)-6-fluoro-1*H*-benzoimidazol-4-yloxy]ethyl}acetamide; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

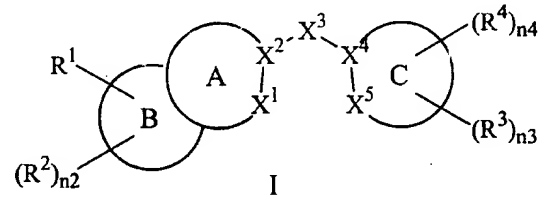
9. The compound of Claim 5 selected from:

2-(4,6-difluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine; and

2-(4-amino-6-fluoro-1*H*-benzoimidazol-2-ylmethyl)-1*H*-benzoimidazole-5-carboxamidine; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers, mixtures of isomers and pharmaceutically acceptable salts thereof.

10. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomer or pharmaceutically acceptable salts thereof, in combination with a pharmaceutically acceptable excipient.

11. A method of treating a disease in an animal in which anticoagulation can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom

optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is –R^6 or –X^6–R^6, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular

atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and X^5 is a heteroatom moiety selected from –N=, –NR^5–, –O– and –S–, wherein R^5 is as defined above, and any carbocyclic ketone, thioketone and iminoketone derivative thereof;

X^3 is –O–, –S–, –C(O)–, –NR^7–, –SiR^7R^8– or –CR^7R^8–, wherein R^7 is hydrogen, (C_{1-6})alkyl or hydroxy and R^8 is –R^6 or –X^6–R^6, wherein X^6 and R^6 are as defined above, or R^7 and/or R^8 together with a free valence on the annular atom adjacent to X^4 forms (C_3)alkylene;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any annular atom with an available valence comprising B;

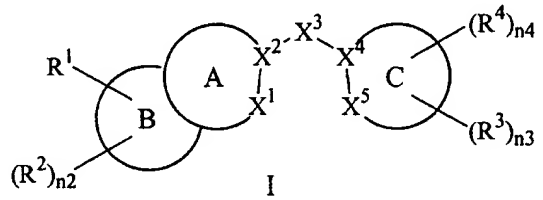
each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently –R^6 or –X^6–R^6, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from (C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo,

hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; with the proviso that R^2, R^3, R^4, R^5, R^7 and R^8 are not all hydrogen and/or (C_{1-3})alkyl when A together with B comprises 1*H*-benzoimidazol-2yl, C comprises 1*H*-benzoimidazol-2yl and X^3 is $-CR^7R^8-$; or a *N*-oxide derivative, prodrug derivative, individual isomer, mixture of isomers or pharmaceutically acceptable salt thereof.

12. A process for preparing a compound of Formula I:



I

in which:

n2 is 1, 2 or 3;

n3 is 1, 2, 3 or 4;

n4 is 1 or 2;

A together with B comprises a fused heterobicyclic radical containing 8 to 12 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^1 and X^2 are adjacent annular members of an aromatic ring and X^1 is a heteroatom moiety selected from -N=, $-NR^5-$, -O- and -S-, wherein R^5 is $-R^6$ or $-X^6-R^6$, wherein X^6 is a linking group containing 1 to 12 contiguous linking atoms and R^6 is hydrogen, (C_{6-14})aryl, cyclo(C_{3-14})alkyl, hetero(C_{5-14})aryl, heterocyclo(C_{3-14})alkyl, hetero(C_{8-14})polycycloaryl or (C_{9-14})polycycloaryl;

C comprises a heteromonocyclic or fused heteropolycyclic radical containing 5 to 18 annular atoms, wherein each ring contains 5 to 7 annular members, each annular atom optionally is a heteroatom, X^4 and X^5 are adjacent annular members of an aromatic ring and

X^5 is a heteroatom moiety selected from -N=, -NR^5-, -O- and -S-, wherein R^5 is as defined above, and any carbocyclic ketone, thioketone and iminoketone derivative thereof;

X^3 is -O-, -S-, -C(O)-, -NR^7-, -SiR^7R^8- or -CR^7R^8-, wherein R^7 is hydrogen, (C_{1-6})alkyl or hydroxy and R^8 is -R^6 or -X^6-R^6, wherein X^6 and R^6 are as defined above, or R^7 and/or R^8 together with a free valence on the annular atom adjacent to X^4 forms (C_3)alkylene;

R^1 is amidino and bonded to any annular carbon atom with an available valence comprising B;

each R^2 is independently hydrogen, (C_{1-3})alkyl, (C_{1-3})alkyloxy, (C_{1-3})alkylsulfonyl, (C_{1-3})alkylthio, carboxy, halo, (C_{2-12})heteroalkyl, hydroxy, mercapto or nitro and bonded to any

annular atom with an available valence comprising B;

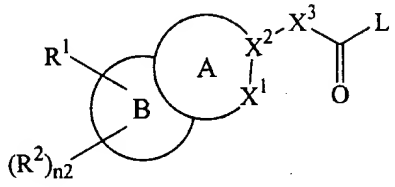
each R^3 is independently hydrogen, cyano, halo, nitro, perhalo(C_{1-3})alkyl or perhalo(C_{1-3})alkyloxy and bonded to any annular atom with an available valence comprising C; and

each R^4 is independently -R^6 or -X^6-R^6, wherein X^6 and R^6 are as defined above, and bonded to any annular atom with an available valence comprising C;

wherein aliphatic or alicyclic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with 1 to 5 substituents independently selected from (C_{1-6})alkyl, (C_{1-6})alkylamino, di(C_{1-6})alkylamino, (C_{1-6})alkylcarbamoyl, di(C_{1-6})alkylcarbamoyl, (C_{1-6})alkyloxy, (C_{1-6})alkyloxycarbonyl, (C_{1-6})alkylsulfinyl, (C_{1-6})alkylsulfonyl, (C_{1-6})alkylthio, amino, carbamoyl, carboxy, cyano, guanidino, halo, hydroxy, mercapto, perhalo(C_{1-3})alkyl, perhalo(C_{1-3})alkyloxy and uriedo; and aromatic moieties with an available valence comprising each X^6 and R^6 optionally are substituted with one to three substituents independently selected from (C_{1-3})alkyl, (C_{1-3})alkylamino, di(C_{1-3})alkylamino, (C_{1-3})alkyloxy, (C_{1-3})alkyloxycarbonyl, (C_{1-3})alkylimino, amino, carboxy, cyano, guanidino, halo, hydroxy, perhalo(C_{1-3})alkyl and perhalo(C_{1-3})alkyloxy; with the proviso that R^2, R^3, R^4, R^5, R^7 and R^8 are not all hydrogen when A together with B comprises 1*H*-benzoimidazol-2yl, C comprises 1*H*-benzoimidazol-2yl and X^3 is -CR^7R^8-; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers,

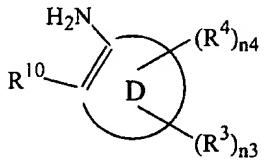
mixtures of isomers and pharmaceutically acceptable salts thereof, which process comprises:

a) reacting a compound of Formula 1:

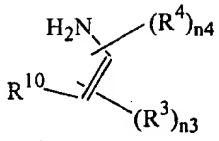


1

with a compound of Formula 2(a) or 2(b):



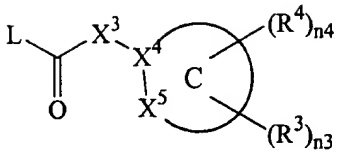
2(a)



2(b)

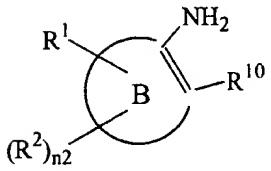
in which L is a leaving group, D together with the vinylene moiety to which it is fused comprises a monocyclic or fused bicyclic divalent radical containing from 5 to 15 annular atoms, wherein each ring contains 5 to 7 annular atoms and optionally one or more annular members is a heteroatom moiety, R^{10} is -OH, -NHR^5 or -SH and heteroatom moiety, n2, n3, n4, A, B, X^1, X^2, X^3, R^1, R^2, R^3, R^5 and R^4 are as defined above, to give a compound of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(b) reacting a compound of Formula 3:



3

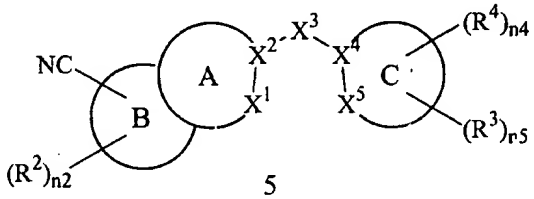
with a compound of Formula 4:



4

in which L is a leaving group, R^{10} is -OH, $-NHR^5$ or -SH and n2, n3, n4, B, C, X^3, X^4, X^5, R^1, R^2, R^3, R^4 and R^5 are as defined above, to give a compound of Formula I in which X^4 and X^5 are adjacent members of an oxazol-2-yl, 1*H*-imidazol-2-yl or thiazol-2-yl ring; or

(c) reacting a compound of Formula 5:



5

in which n2, n3, n4, A, B, C, X^1, X^2, X^3, X^4, X^5, R^2, R^3 and R^4 are as defined above, with hydroxylamine hydrochloride to give a corresponding *N*-hydroxycarboxamidine and then dehydroxylating;

(d) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8C(O)OH$ with a compound having the formula $R^6X^9NHR^9$ to give a compound of Formula I in which R^4 or R^5 comprises $-X^8C(O)NR^9X^9R^6$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8

and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined above;

(e) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9C(O)OH$ to give a compound of Formula I in which R^4 or R^5 comprises $-X^8NR^9C(O)X^9R^6$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined above;

(f) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9S(O)_2Cl$ to give a compound of Formula I in which R^4 or R^5 comprises $-X^8NR^9S(O)_2X^9R^6$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined above;

(g) optionally further reacting a compound of Formula I in which R^4 or R^5 comprises $-X^8NHR^9$ with a compound having the formula $R^6X^9C(O)H$ under reducing conditions to give a compound of Formula I in which R^4 or R^5 comprises $-X^8NR^9CH_2X^9R^6$, wherein X^8 and X^9 are linking groups containing n8 and n9 contiguous linking atoms, respectively, wherein the sum of n8 and n9 is 0 to 10, R^9 is hydrogen or (C_{1-6})alkyl and R^6 is as defined above;

(h) optionally further converting a compound of Formula I into a pharmaceutically acceptable salt;

(i) optionally further converting a salt form of a compound of Formula I to non-salt form;

(j) optionally further converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(k) optionally further an *N*-oxide form of a compound of Formula I its unoxidized form;

(l) optionally further converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(m) optionally further converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

INTERNATIONAL SEARCH REPORT

ernational Application No
PCT/US 98/25216

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D235/20 A61K31/415 C07D403/14 C07D405/14 C07D453/02
C07D413/14 C07D417/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 540 051 A (DAIICHI PHARMACEUTICAL CO) 5 May 1993 see claims ---	1-11
Y	CAUGHEY G H ET AL: "BIS(5-AMIDINO-2-BENZIMIDAZOLYL)METHANE AND RELATED AMIDINES. ARE POTENT, REVERSIBLE INHIBITORS OF MAST CELL TRYPTASES" JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, vol. 264, no. 2, 1993, pages 676-682, XP002064911 see the whole document --- -/--	1-11

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
26 February 1999	18/03/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Henry, J

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	TIDWELL R -R ET AL: "DIARYLAMIDINE DERIVATIVES WITH ONE OR BOTH OF THE ARYL MOIETIES CONSISTING OF AN INDOLE OR INDOLE-LIKE RING. INHIBITORS OF ARGININE-SPECIFIC ESTEROPROTEASES" JOURNAL OF MEDICINAL CHEMISTRY, vol. 21, no. 7, 1 July 1978, pages 613-623, XP000573913 see the whole document	1-11
Y	NAGAHARA T ET AL: "DiBASIC (AMIDINOARY) PROPANOIC ACID DERIVATIVES AS NOVEL BLOOD COAGULATION FACTOR XA INHIBITORS" JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 8, 15 April 1994, pages 1200-1207, XP000608128 see the whole document	1-11
Y	DE 28 39 989 A (HOECHST AG) 3 April 1980 see the whole document	1-11
Y	CHEMICAL ABSTRACTS, vol. 89, no. 17, 23 October 1978 Columbus, Ohio, US; abstract no. 141219c, GERATZ J. ET AL: "SPECIFIC INHIBITION OF PLATELET AGGLUTINATION AND AGGREGATION BY AROMATIC AMIDINO COMPOUNDS" page 129; XP002094821 see abstract & THROMB.HAEMOSTASIS, vol. 39, no. 2, 1978, page 4	1-11
Y	CHEMICAL ABSTRACTS, vol. 94, no. 1, 5 January 1981 Columbus, Ohio, US; abstract no. 232t, TIDWELL R. R. ET AL: "STRATEGIES FOR ANTICOAGULATION WITH SYNTHETIC PROTEASE INHIBITORS. XA INHIBITORS VERSUS THROMBIN INHIBITORS" page 237; XP002094822 see abstract & THROB. RES., vol. 19, no. 3, 1980, pages 339-349,	1-11

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INTERNATIONAL SEARCH REPORT

rnational Application No
PCT/US 98/25216

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	TIDWELL R.R. ET AL: "AROMATIC AMIDINES: COMPARISON OF THEIR ABILITY TO BLOCK RESPIRATORY SYNCYTIAL VIRUS INDUCED CELL FUSION AND TO INHIBIT PLASMIN ,UROKINASE THROMBIN, AND TRYPSIN" JOURNAL OF MEDICINAL CHEMISTRY., vol. 26, no. 2, 1983, pages 294-298, XP002094820 WASHINGTON US see the whole document	1-11
P,X	WO 98 45275 A (AXYS PHARMACEUTICALS CORPORATION) 15 October 1998 see claims	1-11
P,X	US 5 693 515 A (CLARK JAMES M ET AL) 2 December 1997 see the whole document	1-11
P,X	WO 98 01428 A (THE DU PONT MERCK PHARMACEUTICAL COMPANY) 15 January 1998 see claims	1-11

1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 98/25216

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 11
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 11 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: NOT APPLICABLE
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: NOT APPLICABLE

In view of the extremely broad Markush claims,the search was executed with due regard to the PCT Search Guidelines(PCT/GL/2),C-III,paragraph 2.1,2.3 read in conjunction with 3.7 and rule 33.3 PCT,i.e. particular emphasis was put on the inventive concept,as illustrated by:
The compounds of claims 3-9 and particularly the compounds of the examples
The international search was in so far as possible and reasonable complete in that it covered the entire subject-matter to which the claims are directed.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

rnational Application No
PCT/US 98/25216

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0540051 A	05-05-1993	AT 136293 T	15-04-1996
		AU 666137 B	01-02-1996
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